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A TREATISE ON

MATERIA MEDICA,

(Including Therapeutics and Toxicology.)

BY

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Prof. of Medicine in the University of Jena,

AND

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VOL. III.

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BERMINGHAM & COMPANY,

28 UNION SQUARE, EAST, NEW YORK.

20 KING WILLIAM STREET, STRAND, LONDON.

1884.

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PUBLISHERS' NOTICE.

Owing to the press of professional duties, Drs. HEINEMAN and BERG were unable to complete the translation of this work in time to place it in this series. The publishers were therefore compelled to secure the services of Dr. VALENTINE, who kindly completed the translation, his work beginning on page 600.

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CONTENTS.

BITTER PRINCIPLES OF FEEBLE PHYSIOLOGICAL ACTION, 571
Gentian root, 574
Bitter clover, 574
Herba centaurii, 575
Millefolia, 575
Quassia, 575
Taraxicum, 575
Cardui benedictus, 576
Iceland moss, 576
Colombo, 576
Simaruba, 577
Polygala amara, 577
Farfara, 577
Galeopsidis, 577
Phlorrhizin, 577
Ox bile, 577
Condurango, 577
THE CYANOGEN COMPOUNDS, 578
Hydrocyanic acid, 579
Bitter almond water, 585
Cherry water, 585
Cherry laurel water, 585
Bitter almonds, 585
Cherry laurel, 585
THE ALKALOIDS, 585
Alkaloids of cinchona, 590
Quinine, 590
Cinchonine, 591
Dichonquinine, 591
Cinchonidin, 591
Dicinchonin, 591
Chinovin, 591
Kinic acid, 591
Kinotannic acid, 591
Sulphate of quinine, 614
Muriate of quinine, 615
Bisulphate of quinine, 615
Citrate of iron and quinine, 615
Tannate of quinine, 615
Valerianate of quinine, 615
Cinchonia, 615
Sulphate of cinchonia, 615
Chinioideum, 615
Chonchinine, 615
Tincture cinchona, 616
Wine of cinchona, 616
Bebeerine, 616
Piperine, 616
COFFEE, TEA, GUARANA, COCOA, AND COCA, 616
Caffein, 617
Coffee, 624
Chinese tea, 628
Paraguay tea, 629
Guarana, 629
Theobromine, 629
Chocolate, 630
Cocoa, 630
Cocaine, 630
Coca, 635
THE ALKADOIDS OF OPIUM, 635
Morphine, 636
Muriate of morphine, 660
Acetate of morphine, 660
Sulphate of morphine, 660
Narcotine, 660
Narceine, 661
Codeine, 661
Thebaine, 662
Thebenine, 662
Rhœadine, 662
Apomorphine, 662
Opium, 662
Extract of opium, 669
Compound ipecac powder, 669
Tincture opium, 669
Laudanum, 669
Paregoric, 669
Cannabis indica, 671

Lactucarium, 674
Lupulin, 674
Gelsemium sempervirens, 675
Coto-bark, 678
Quebracho, 679
Apomorphine, 681
Emetine, 684
Ipecac, 686
Colchicine, 689
THE ALKALOIDS OF BELLADONNA, STRAMONIUM, AND HYOSCYAMUS, 690
Atropine and belladonna, 692
Hyoscyamine, 708
Stramonium, 709
THE ALKALOIDS OF CALABAR BEAN, JABORANDI, AND THE TOADSTOOL, 710
Physostigmine, 712
Calabarin, 720
Pilocarpine, 720
Muscarine, 725
THE ALKALOID OF TOBACCO, 729
Nicotine, 729
Tobacco, 734
Lobelia, 738
Curare, 739
Conium, 746
Sparteine, 746
THE TETANIC ALKALOIDS OF STRYCHNOS, IGNATIUS, AND OPIUM, 747
Strychnine, 747
Nux vomica, 747
Veratrine, 758
Aconitin, 767
Staphisagria, 767
GLYCOSIDES WITH STRONG PHYSIOLOGICAL ACTION, 769
Digitalis purpurea, 771
Squills, 782
Adonis vernalis, 783
Green hellebore, 783
Senega, 783
Saponine, 783
Picrotoxin, 786
Solanin, 787
PROTEINE MATTERS, 787
Albumen and peptone, 787
Meat, 793
Eggs, 795
Blood, 796
Milk, 796
Condensed milk, 798
Whey, 798
Pepsine, 800
Pancreatine, 801
GLUTINOUS SUBSTANCES, 801
White glue, 803
GLYCERINE AND FATS, 803
Glycerine, 803
Fats, 807
Butter, 814
Lard, 814
Tallow, 814
Cod liver oil, 814
Beeswax, 818
Cetaceum, 818
Olive oil, 818
Almond oil, 818
Poppy oil, 819
Hemp oil, 819
Linseed oil, 819
Lycopodium, 819
Vaseline, 819
THE CARBO-HYDRATES, 820
Sugar, 820
Cane sugar, 822
Sugar of milk, 823
Grape sugar, 823
Maple sugar, 823
Honey, 823
Licorice, 823
Carrot, 824
Couch-grass, 824
Starch, 824
Arrowroot, 826
Dextrin, 826
Vegetable mucus and gum, 827
Salep, 828
Marsh, mallow, 828
Carrageen, 828
Gum arabic, 829
Tragacanth, 829

BITTER PRINCIPLES OF FEEBLE PHYSIOLOGICAL ACTION.

UNDER this head are included a variety of indifferent crystallizable vegetable substances and their mother plants, all of which are non-nitrogenous, but of unknown constitution and unimportant physiological action. We cannot simply term these substances bitter principles (amara), for under this head would be included a large number of substances having the most heterogeneous action; thus, here would be included the bitter alkaloids, glucosides, etc. We have therefore added the characteristic "of feeble physiological action" to the title of this class of substances; we have not included such substances as picrotoxin, cantharadin, santonin, cossin, etc., to this group because of the great difference in the physiological action of these substances and those to be included under the above heading. The bitter principles like gentiopicrin, quassin, menianthin, etc., have such a resemblance in their physiological action that we may infer a similar chemical identity. The mother plants from which these substances are derived do not contain any more active materials, and therefore will not in this respect create any confusion. The plants which contain strong ethereal oils have been relegated to the domain of spices and flavoring agents

PHYSIOLOGICAL ACTION.

The physiological action of these substances can be considered in a group.

Upon the lowest organisms the bitter principles have a decidedly injurious action, as we have convinced ourselves by our own investigations; but much larger doses than of the phenols are necessary. They prevent fermentation and decomposition when given in these larger doses. The formation of carbonic acid in fermenting sugar solutions was

diminished by weak solutions of phlorrhizin, while salicin caused an increase in the quantity of carbonic acid formed. Some of these bitter principles—quassin, for instance—have a narcotic action upon flies.

When taken they produce a bitter taste in the mouth which lasts for some time. This bitter taste is much less intense than that of strychnine, quinine, etc. Buchheim and Engel have shown that the tartrate of strychnia has a bitter taste even in 1-48000 dilution; tartrate of quinine, 1-10,000; tartarate of cinchonine, 1-4000; tartrate of morphine, 1-2000; salicin, 1-1500; phlorrhizin, 1-500. We do not know upon what alterations in nerves of taste this bitter taste depends.

As a reflex result of the bitter taste we have increased excretion of saliva.

In the same manner the secretion of the gastric juice is probably also increased when these bitter principles are introduced upon an empty stomach. Even small doses give rise to a peculiar feeling in the stomach, which is identified as similar to that of hunger, although, according to Griesinger, this pain (?) must be distinguished from that of hunger. Larger doses produce real gastric pain, and even digestive disturbances. Very large doses cause vomiting.

It has not been proved that there is any increase in secretion of the gastric juice. On the contrary, we would suppose that the spices would, from their very nature, be more active in this respect than the bitter principles, hence we should prefer these as appetizers, since besides being more effective they have also a more agreeable taste.

As far as the digestion is concerned the experiments of Buchheim and Engel have shown that the presence of bitter principles does not cause any more rapid or greater conversion of albumen into peptone or starch into sugar, nor did they observe any increase in the biliary excretion.

We have, therefore, no reason for supposing that these bitter principles can in any way improve the digestion or appetite in healthy people.

In the diseased stomach we know from experience that the digestion improves on the administration of the bitter principles. But since these are never given alone it is uncertain how much of the effect is due to the other substances given with the bitter principles. We have no doubt *that when the bitter* principles are given with the ethereal

oils, or with alcohol (bitter tinctures), the effect is due for the most part to the two latter agents, for even the antifermentative power of the ethereal oils and alcohol is greater than that of the bitter principles. It is true that the hypothesis of Traube, that perhaps the blood pressure is increased under the influence of the bitter principles, and that hence the secretion of the gastric juice is increased, seems to have been confirmed by the observation of H. Köbler that the injection of solutions of the bitter principles into the jugular vein results in a temporary decline followed by a rise in blood pressure; but it is not certain that a similar result would follow the administration of such solution by the stomach.

THERAPEUTIC APPLICATION.

Apart from a few conditions in which individual members of the group of bitter principles are used, the only general indication for their use is dyspepsia. The best results are attained in the "atonic dyspepsia," which is evidenced by the following clinical history. The patients feel no discomfort in the region of the stomach, the tongue is not coated, there is no fever, but only very marked loss of appetite. They are also well given in the apepsia following acute febrile diseases, which are also generally characterized as "atonic;" indeed, in all cases in which the dyspepsia is accompanied by a certain degree of anæmia and none of the symptoms of gastric catarrh. Thus the bitter tonics combined with iron are useful in chlorotic patients, and in those who have lost their appetite from any kind of excess or nervous excitement. They are also excellent remedies for the dyspepsia of drunkards.

The above-mentioned drugs are not given in plethoric individuals; they are directly injurious in organic diseases of the stomach, especially in ulcer and carcinoma; also in slighter catarrhs where the tongue is coated and there are other symptoms of a catarrhal affection. The older physicians have shown that these drugs are of value in the so-called "irritable weakness of the stomach," where there is a tendency to cardialgia, and where there is great sensitiveness of the stomach, with frequent vomiting. In the digestive disturbances of the hysterical and hypochondriacs, they are seldom well borne.

No other application of the bitter principles is made; they

are useless as febrifuges and anthelmintics. They must often be combined with quinine, iron, light aromatic preparations, and alcohol (in the form of tinctures). The whole of the good effect, however, does not depend upon these adjuvants, for it is observed even if the cold infusion is given. In order to get a good effect it is necessary that the drug be used for a long time, and that it be not used in too large doses, for large doses often accomplish a reverse effect from that desired.

Experience has shown that the form under which bitter principles are given has a great influence upon the effect. The best form is that of the cold infusion; the next best the extract. The tinctures are very good in some cases where the condition of the stomach does not prohibit the use of alcohol. The decoction is less effective than the cold infusion; the worst form is that of the powder.

Gentian root—radix gentianæ rubræ, from gentiana lutea, contains a glucocide, bitter principle, which is readily soluble in water and alcohol, namely, gentio-picrin, $C_{20}H_{30}O_{12}$, which is decomposed by boiling with weak acids into sugar and gentio-genin, $C_{14}H_{16}O_5$. There is also found an acid, gentianic acid, sugar, and a trace of ethereal oils.

Gentian has the most powerful antiseptic action of any of the above-mentioned materials. In addition to its bitter taste, it has the effects described in the introduction. Large quantities disturb the digestion and are said to cause headache, redness of the face, and unconsciousness. When it is injected directly into the blood no pathological symptoms occur. We have no reliable observations.

Gentian is a drug which is very much used under the circumstances given above. Formerly it was held as quite a febrifuge, and before the introduction of quinine it was one of the most popular agents. But it does not seem to have any such power, and now it is only used as a popular remedy. It is no more useful as an anthelmintic.

Dosage and Preparation.—1. Radix Gentianæ in watery or vinous infusion or decoction, from 5.0–10.0 : 200.0.

2. Extract, gentianæ, of thicker consistency, of a brown color, and soluble in water. From 0.1–0.5 pro dosi, in pill or solution.

3. Tinctura gentianæ; 1 part of the root to 6 parts of alcohol—yellowish-brown, from 25–30 drops pro dosi (1.0–3.0).

4. Tincture amara, 3 parts each of radix gentianæ, herba centaurii, fructus aurantii immaturi, and 1 part of rhizoma zedoariæ to 315 parts of alcohol—of a brown, light-green color—in the same dose.

Radix gentianæ also forms a component of various tinctures and elixirs.

Bitter clover (fever clover) leaves—Folia trifolii fibrini—is a trifoil of the gentian group, menyanthes trifoliata, and contains an amorphus substance, menyanthin, $C_{26}H_{46}O_4$, readily soluble in alcohol and hot water, which, when heated with a dilute acid, is decomposed into sugar and a bitter oil, having an almond odor—menyanthol. Used like gentian.

Dosage and Preparations.—1. Folia trifolii fibrini, in the same form as gentian.

2. Extract trifolii fibrini; thick, dark-brown extract; soluble in water. From 0.5–2.0 pro dosi, in solution or pill.

Herba centaurii—of gentianee erythræa centaurium—contains a non-isolated bitter principle; has a slightly cathartic effect, otherwise like bitter clover. Dose and preparation like those of bitter clover.

Herba et flores millefolia—contain a not disagreeable, bluish ethereal oil, a glucoside bitter principle achillein, and relatively many salts. We know little of its physiological action.

Herba and extractum millefolii are the officinal preparations, and are therapeutically of little importance. Much used in popular therapy.

Quassia wood—lignum quassiæ, known as bitterwood, from quassia amara, which contains a crystalline neutral bitter principle, quassin, $C_{10}H_{12}O_3$, readily soluble in alcohol, with difficulty in water. When heated it burns like a resin.

When smaller insects drink infusions of this substance they are narcotized without being killed. Otherwise, little is known of its physiological action, and, according to Husemann, 3.0 grm. of the extract were without effect upon dogs.

As far as its therapeutic application is concerned, quassia resembles in every way the above-mentioned remedies. The remarkable results expected from it have not been seen, and since the drug is no more effective than other remedies like gentian, while it is much more expensive, it should be omitted in our list of drugs.

Taraxacum root and leaves—Radix et herba taraxici, from taraxacum-officinali—contains in all its parts a bitter principle, taraxacin, and many potassium and calcium salts. Its juice also contains resinous bodies. In the spring the plant contains more salts and less bitter principles; in the autumn the reverse.

The plant has a slightly cathartic effect. It is generally used in combination with other plants.

Preparations.—Extractum Taraxaci, a thick, dark-brown soluble extract. Used chiefly as a constitutent of pill masses.

The expressed juice of taraxacum is one of the constituents of the "succi recenter expressi" used formerly as "alteratives" in spring. It is now replaced by the mineral waters. The good effect of this juice was due to the percentage of potash and sodium salts contained in the plant in early spring. The juices of the following plants were used for these spring cures:

Taraxacum (radix et herba), fumaria (herba), cichorium (radix) carduus benedictus (herba), trifolium fibrinum (herba), millefolium (summitates), cochlearia, nasturtium aquaticum, ruta, cerefolium, saponaria (herba), gramen (radix) chelidonium majus (herba). The juice of very young plants disturbs digestion very much, because it contains too little of the bitter components. 30–50 grms. of the older plants produce the effect of the bitter principles; 100–150 grm. a slightly cathartic effect. 50.0–100.0 grm. of the juice can be taken in the morning upon an empty stomach, and thus the digestion regulated.

The conditions to be relieved by these "spring cures" were very various, and generally those of plethora abdominalis. It is probable that they are of some use in this condition, although the "cure" must be aided by proper diet, etc. We should be careful not to produce digestive disturbances from the too long-continued use of these drugs.

These herbs should always be taken in fluid form.

These herb juices are used in moderate chronic constipation and its sequelæ which occur in sedentary people, when the mineral waters are contra-indicated on account of a weak constitution; also when there is a slight degree of atonic dyspepsia, with no gastric catarrh as its cause.

The formerly popular species ad clysmata visceralia Kæmpfii are to-day no longer used.

Folia cardui benedicti—from cnicus benedictus—contains a bitter principle, cnicin, $C_{42}H_{46}O_{16}$, which is readily soluble in hot water and alcohol; also large quantities of alkaline salts.

The presence of cnicin produces the effects of the other bitter principles; the salts cause diuresis and diarrhœa, when the leaves (infusion) are given in large quantities.

Therapy, dose, and preparations exactly like those of trifolium fibrinum.

Iceland moss—lichen islandicus, from cetraria islandica—has a bitter mucilaginous taste, and contains two bitter acids, which crystallize in white needles. They are cetraric acid, $C_{18}H_{16}O_8$, with difficulty soluble in cold water and alcohol. Soluble in alkalies and lichen stearic acid, $C_{14}H_{24}O_2$. It also contains 10 per cent of a starch (turning blue under iodine), and lichenin (20 per cent), a starch which swells up in water and does not react with iodine.

Physiologically it acts like other bitter principles. It may be looked upon as a food, on account of the starch which it contains.

Therapeutically, Iceland moss is entirely superfluous; but, since it is still ordered by some physicians, we shall discuss it.

Moss is used as a nutritive and bitter principle. As far as its nutritive properties are concerned, we can get more nourishment from bread; and as a bitter it can be used in the digestive disturbances spoken of above.

This plant has quite a reputation in phthisis and broncho-blenorrhœa. The older physicians (Stoll, etc.) recommend it in these conditions. But reliable observers have long ago shown that in pulmonary consolidations or abscess it is of little use, and experience has shown that its only utility is when an atonic dyspepsia accompanies phthisis, then it acts like other bitter principles.

Dosage and Preparation.—1. Lichen islandicus prepared as a tea for the patient; 1 tablespoonful to two cups of water. In infus. or decoct. 15. 0—25. 0 : 200. 0. A "mucilage" is used, but is an expensive nutritive substance. (30. 0 : 200.0)

The officinal preparations are: 2. Lichen islandicus ab amaritie liberatus. Superfluous, contains starch only.

3. Gelatina lichenis islandicis in Z.—zss, doses.

4. Gelatina lich. isl. saccharata sicca.

Colombo root. Radix colombo from jateorrhiza colombo, etc., contains a bitter principle columbin $C_{21}H_{22}O_7$, which crystallizes in white needles, and a bitter acid, columbic acid, an alkaloid berberin, $C_{20}H_{17}NO_4$ and a large quantity of starch. (33 per cent.)

Columbin has no effect upon men and animals when given in doses, 0.1 grm. (Schroff and Falck); berberin when injected directly into a vein has a fatal effect upon animals (rabbits and dogs); producing before that however salivation, nausea, vomiting, diarrhœa, difficult breathing, tremor, and finally paralysis, in doses from 1.0–3.0 grm.; when given internally it produces painless diarrhœa (Falck).

We do not therefore see any signs of a constipating effect from the

action of the components of columbo root—20 grm. (infusion of the root) produced in H. Köhler vomiting, rumbling and pain in the abdomen and loss of consciousness; the nausea continuing for 24 hours.

Colombo root is given (in decoction) like the amara in digestive disturbances. Also in the habitual diarrhœa of children which follows dysentery. Also in the diarrhœa of phthisis, when there are no considerable ulceration processes going on.

We ourselves formerly used the remedy very much; but no longer for the last few years, and do not miss it, and therefore consider it superfluous.

Dosage and Preparations.—Radix columbo in decoction from 10–15. : 200 grm.

2. Extractum columbo, a yellowish brown powder with difficulty soluble in water, and only active as a bitter principle, from 0.3–1.0 in pill or mixtures.

Appendix to Bitter Principles.

Among the bitter principles no longer used are cortex simarubæ, herba polygalæ amaræ, folia farfaræ, and herba galeopsidis.

Also phlorrhizin, which is obtained from the roots of apple and plum trees. Salicin has already been considered, and the orange, lemon, cascarilla bark, calumus, and vermuth have been studied under flavoring agents and spices.

Ox bile—fel tauri (bilis bovina)—was formerly classed among the bitter principles on account of its bitter taste, although chemically, physiologically, and therapeutically they have nothing in common with this. When introduced into the stomach it causes digestive disturbance by neutralizing the acids of the stomach and precipitating the pepsin; in consequence of which it causes nausea and vomiting. Therapeutically it is entirely useless. There is no condition in which it is of the slightest utility. 1. Fel tauri inspissatum from 0.5–2.0 pro dosi 2–fel tauri depuratum siccum from 0.3–0.6 pro dosi.

Condurago rind.—Cortex condurago, the rind of one of the varieties of the macroscepis, a parasitic plant of the Andes, and in the fresh state has an odor resembling that of cascarilla and pepper, and a somewhat bitter taste. In 100 parts of rind there are 80 parts of a vegetable substance which consists of a yellow resin soluble in alcohol, tannin, a fat, yellow and brown coloring matters, starch and cellulose. It contains no alkaloid or volatile oil (antisell). Various authorities differ as to its physiological action, possibly on account of the varying size of the dose and possibly on account of the use of different preparations. According to Gebe there are three varieties of condurago rind—that of Venezuela (micania guaco), that of Ecuador, and condurago madeperro; the last is the most effective. According to Renzi condurago has no physiological action. According to De Sanctis it produces a temporary excitement followed by a depression of the nervous system. According to Palmesi it causes in cold and warm-blooded animals anæsthesia, dyspnœa, heart paralysis and death. According to Giannuzzi the concentrated decoction has no irritating action upon the mouth, stomach or intestinal mucous membrane. The spinal cord, on the other hand, becomes greatly irritated, and there are intense tetanoid spasms. The brain does not appear to suffer, the animals remain conscious until death; the heart, muscles and iris are not affected. Relatively small doses have, as Riegel first observed, a decidedly improving effect upon the appetite, without disturbing any

other functions. Hedde observed increased excretion of urine. We place condurago provisionally among the bitter principles for want of a more acceptable classification.

Therapeutic Application.—In 1871 and '72 American, Italian, and English physicians made experiments with condurago in the treatment of cancer, without achieving the wished-for result. In Germany the drug began to be used in 1874, when Friedrich reported what appeared to be a case of carcinoma ventriculi cured by condurago. But all other attempts since this have resulted in failure, but recently Drszewezky and Erichsen report cases in which the careful diagnosis of carcinoma ventriculi was made, and in which a retrograde degeneration of the growth took place, so that it disappeared and the patient improved.

Rossbach also reports a case of sarcoma ventriculi in which large doses of this drug caused the disappearance of one of two tumors that were present while all other symptoms improved. But the patient died, and in the situation where the tumor had disappeared was formed a hard connective tissue layer. Riegel, Hedde, Nothnagel, etc., have not observed any disappearance of the growth, but only improvement in the appetite, digestion, and general health.

The fact that we have no other remedy for carcinoma ventriculi seems to render it our duty to try the remedy in every case. In epithelioma of the forehead, eyelids, and nose immediate improvement has been seen to set in on the internal and external use of condurago.

Dosage.—15.0 grms. are macerated for 12 hours in 300 grms. of water and then boiled down to 150 grms. Of this a tablespoonful 2 or 3 times a day is given. Or we might use ext. condurago 0.1 pro dosi 5–10 times a day in pill form (7 parts of cortex to one part of ext. aquos. sicc.).

THE CYANOGEN COMPOUNDS.

By the term cyanogen we mean a combination of carbon and nitrogen, CN=Cy—most of the cyanogen compounds are powerful poisons, and resemble prussic acid HCN in their effects; some have no poisonous effects, while of many the physiological action is unknown.

Cyanogen gas C_2N_2 has a similar but weaker effect than prussic acid. (Laschkewitz, Bunge.)

The most of the metallic cyanides also act like hydrocyanic acid. Thus potassium cyanide, ammonium cyanide, magnesium cyanide, calcium cyanide, mercuric cyanide, lead cyanide, zinc cyanide, copper cyanide, etc. (Pelikan.)

Those metallic cyanides which do not give off hydrocyanic acid, on the addition of dilute acids, are entirely non-poisonous. They are the ferric and ferrous cyanides, the cyanide of platina, as well as the potassio ferrous and ferric cyanides, the cyanides of magnesium and platina, and potassia and platina. (Emmert, Schuebarth, and Pelikan.)

Pelikan's assertion that ethyl and amyl cyanides act

like hydrocyanic acid, while methyl and butyl cyanides are non-poisonous, needs further confirmation. Perhaps those of the former which he examined were impure from admixture with hydrocyanic acid. Rossbach found that 5.0 grm. of perfectly pure ethyl cyanide introduced into the stomach produced no trace of hydrocyanic poisoning, but only signs of a severe gastroentritis (vomiting and diarrhœa) which killed the animal in thirty-six hours. Rabbits, in whom 2.0–grm. of the same preparation were injected subcutaneously, showed no signs of any effect, and remained healthy. So that the results of Hermann's experiments would thus seem to be refuted.

HYDROGEN CYANIDE OR PRUSSIC ACID—ACIDUM HYDROCYANICUM.

Hydrocyanic acid HCN is obtained in a pure state by the distillation of metallic cyanides with the stronger acids. It is also obtained from the bitter almonds, and various kernels when these are allowed to stand for some time in water at a moderate temperature. The amygdalin $C_{20}H_{27}NO_{11}$ is then decomposed by the fermentation of an albuminoid substance also present, emulsin into prussic acid, sugar, and oil of bitter almonds, the elements of water being taken up as follows:

$$\underset{\text{(amygdalin)}}{C_{20}H_{27}NO_{11}} + 2H_2O = \underset{\text{(prussic acid)}}{HCN} + \underset{\text{(sugar)}}{2C_6H_{12}O_6} + \underset{\text{(oil of bitter almonds)}}{C_7H_6O}$$

Both the amygdalin and emulsin are non-poisonous; but when introduced simultaneously into the body, as when bitter almonds are eaten, or when injected into the blood, etc., they develop the poisonous prussic acid and may thus become fatal.

Prussic acid is a light colorless fluid, which crystallizes at −15°C, and boils at +26°. It evaporates even at ordinary temperature and thus produces cold. Its acid properties are very slight; it scarcely reddens blue litmus; its odor is that of bitter almonds.

Prussic acid cannot be long kept; it decomposes with the formation of ammonium salts; the addition of a trace of strong acid and great dilution with water are apt to retard this decomposition.

The officinal prussic acid preparation, the aqua amygdalarum amarum, and lauro cerasi can only contain 0.1 per cent of prussic acid.

Physiological action.—Prussic acid is the most fatal of all poisons, especially for warm-blooded animals; small animals die after the inhalation of the smallest unappreciable quantities; small birds, guinea pigs, etc., die after inhaling only a trace of the acid for a second. Adult persons and the larger animals die from 0.06 grm., that is one drop of anhydrous prussic acid. Cold-blooded animals (frogs and fish) are affected less readily than warm-blooded. It is not true that leeches are unaffected by prussic acid.

The acid is absorbed into the organism very rapidly; less readily through the unbroken skin, more rapidly by the mucous membranes, or when injected hypodermically, and most rapidly after direct injections into the blood, or when inhaled. Because prussic acid kills so quickly, it was supposed that it exerted its paralyzing effects upon the nerve

centres by passing along the peripheral nerves, and not by passing through the circulation. But Krimer and Preyer have shown that prussic acid always requires at least fifteen seconds of time before it produces death or symptoms of poisoning; in other words, the exact amount of time required for the blood to circulate around the body. Furthermore, death or poisoning sets in even when the nerves passing from the effected part are cut, and does not set in when the vessels are tied so as to prevent the passage of the poisoned blood into the system. There is therefore no longer any doubt that, for prussic acid to produce a poisonous effect, it must be absorbed into the circulation and pass through it to the central nervous system.

Disposition and effect of prussic acid in the organism. According to Hoppè Seyler prussic acid differs from all other acids in its effects upon the organism. All other acids destroy hæmoglobin, while prussic acid deposits neither the albuminoids or alters hæmoglobin. The crystallization of hæmoglobin from solutions of the blood corpuscles of the dog is in no way affected by prussic acid. The blood crystals obtained from blood containing prussic acid have the crystallographic and optical properties of normal blood crystals, but contain prussic acid in relatively firm chemical combinations,—for instance, can be repeatedly crystallized out of watery solutions, dried under the air pump and subjected to 0° temperature without undergoing decomposition (which is not the case with normal hæmoglobin) and without losing its percentage of prussic acid. Solutions of prussic acid hæmoglobin crystals, according to Hoppè Seyler show the absorption bands of oxyhæmoglobin in the spectrum ; nor does such hæmoglobin show any signs of reduction even after months. According to Preyer, who confirmed all of the above statements, prussic acid enters into combination with reduced hæmoglobin as well as with oxyhæmoglobin, but the former can then no longer be converted into oxyhæmoglobin, even where brought in contact with oxygen. Nor does prussic acid hæmoglobin have the property of turning guiac blue, like ordinary oxy or carbonic oxide or nitrous oxide hæmoglobin.

According to Gaethgens, deoxidized blood subjected to the action of prussic acid does not lose its property of absorbing oxygen. On the other hand, oxygenated blood which has been subjected to the action of prussic acid no longer gives up its oxygen to surrounding media, even such as are reducing in their action, nor does blood give up its carbonic acid, to media which attract carbonic acid when subjected to prussic acid.

The above alterations were only seen where blood taken directly from the body is mixed with the prussic acid. In the blood of animals poisoned by prussic acid Preyer saw none of these alterations, or any spectroscopic changes, such as are reported by Hiller ; we cannot, therefore, suppose that death and poisoning by prussic acid is due to any such changes as those reported above. Indeed, even if prussic acid hæmoglobin were thus formed in the body, the quantity of the acid is too small to affect any large proportion of the blood.

Schœnbein has proved that even small quantities of prussic acid suspend the catalytic power of the blood upon hydrogen peroxide ; while freshly drawn ox blood diluted with two volumes of water, decomposes hydrogen peroxide into water and oxygen, the addition of a few drops of prussic acid to the blood suspends the power, and the blood is turned to an opaque brown. The browning of the blood can be recognized with

$\frac{1}{50000}$th part of prussic acid. But even the blood circulating in the living body has not the power of decomposing hydrogen peroxide (Asmuth), and only obtains this power outside of the body. We can make no more use of Schœnbein's than of Hoppè Seyler's observation in determining the real cause of the prussic acid action upon the living body.

When animals are poisoned by prussic acid, the venous blood of both cold and warm blooded amimals becomes of clear red color, like normal arterial blood (Cl. Bernard). In warm blooded animals, the bright coloring of the venous blood sets in simultaneously with the beginning of the diminution in blood pressure (Rossbach); in the same moment that the spring of the manometer connected with the carotid sinks, the jugular vein becomes enormously swollen with the bright red blood coming down from the brain. At the same time the animal falls into convulsions and coincidently the venous blood of the whole body becomes of a bright red. This reddening occurs even in frogs lying under oil, and in warm-blooded animals whose respiration has been in every way limited. While in frogs this lasts for many hours after death, in warm-blooded animals it disappears very rapidly, and the venous blood becomes even darker than before.

The respiratory interchange of gases is altered, according to Gaethgens, to this extent, that in the beginning of the poisonous action, that is just when the bright red blood streams through the veins, less carbonic acid is exhaled, and less oxygen is taken up by the blood, than in the normal state, in a compensatory manner, the oxidation processes become extraordinarily energetic; and thus the first bright red, and later dark, color of the venous blood would be explained. Gleinitz, Preyer, on the other hand, have explained the bright red color of the venous blood by supposing that the blood corpuscles (in cold-blooded animals) become rounded punctated and therefore reflect more light.

Although the above observations of Gaethgens render it highly probable that the living blood also undergoes alteration, under the influence of prussic acid, we cannot consider these alterations the cause of the poisonous action of prussic acid, any more than we can consider the prussic acid dyspnœa as due to the prevention of the interchange of gases which is due to this agent; for Herrmann has shown that frogs, which are insensible to carbonic acid, still die from the effects of prussic acid. We must, therefore, consider that the chief effect of prussic acid is due to its action upon the nerve substance. All nerves which are placed in prussic acid solutions die rapidly, although we do not know exactly from what cause. Wallach thinks that the effect of prussic acid is to be accounted for in a manner somewhat similar to that laid down by Binz as the method of the physiological action of arsenic, phosphorus, etc.

We do not know what alterations the prussic acid which is absorbed undergoes. Some assert that it can be smelt in the expired air. Preyer thinks that it is positively excreted with the expired air unchanged. Schauenstein, however, has shown in a young man who poisoned himself with prussic acid that the whole of the prussic acid absorbed was converted into ammonium formate. Most other observers, however, proved the presence of prussic acid as such for days afterwards.

The Symptoms of Poisoning.—These are exactly alike in warm-blooded animals and men; in cold-blooded animals they differ from those in warm-blooded animals. Preyer says that a "toleration" for the poison cannot be attained; on the contrary, increased administration results in increased sensitiveness to the poison.

Locally, prussic acid (2 per cent solution) used to moisten the skin causes numbness and anæsthesia. When a frog's leg is dipped in it it gives no sign of any reflex power. (Robiquet and Preyer.)

Mucous Membranes.—Anhydrous prussic acid has a bug-like odor (Caullon); the diluted acid the odor of bitter almonds; upon the tongue and in the throat there is at first a bitter taste, a burning, scratching sensation in the throat, increased salivation, and a feeling of numbness, followed by warmth of the stomach. Upon the cornea the concentrated acid causes opacities and eschars.

Very small doses (0.001 grm.) taken once a day cause in men only local effects upon the mucous membranes; but when taken or inhaled for a long time they produce the following general symptoms: nausea, vomiting, fulness in the head and headache, a feeling of anxiety and pressure over the chest, heavy breathing and slowing of the heart's action. Larger but non-fatal doses (0.01 grm.) cause severe dyspnœa and choking, a high degree of muscular weakness, dilatation of the pupil, anæsthesia, complete loss of consciousness, and general convulsions (tonic and clonic).

After fatal doses (of 0.05 grm.) the tonic convulsions become very severe, so that urine, fæces, and even semen are passed involuntarily. There is complete collapse, with signs of choking; the skin is cold and covered with perspiration; there is general cyanosis, protrusion of the eyeballs, and finally death.

The duration of the poisoning varies with the size of the dose. Very large doses, indeed, may give rise, not to muscular weakness, convulsions, etc., but in 15 to 30 seconds to sudden death; here there is a loud cry, the patient falls, consciousness and sensation are entirely lost, the pupils are dilated; there is no trace of convulsions; respiration is labored and slow, the face cyanotic, and death follows in from 1 to 5 minutes.

In frogs, as in warm-blooded animals, there is paralysis of respiration, protrusion of the eyeballs, diminished reflexes and muscular irritability, but never convulsions.

Influence Upon the Individual Organs and Functions—Nerves and Muscles.—The most affected portion of the central nervous system is the respiratory centre of the medulla; it is first irritated, then paralyzed. The following are the observations of Boehm and Kine on cats, which we have confirmed for dogs and rabbits, and which hold good even in men. Immediately after the injection of prussic acid a few laborious, then rapid respiratory movements occur in which the expiration has a convulsive character. This is followed by a general tonic convulsion, and also an inspiratory spasm. Except during the tetanoid stage there is never observed an inspiratory convulsion.

After large doses the animals die during this inspiratory spasm, while after small doses they survive; the spasm is suspended, a long interval between the respirations sets in; these are followed at long intervals by weak, sighing inspirations, until finally a definite fatal paralysis of respiration sets in. Non-fatal doses are followed by constantly increased frequency of respiration. Section of the vagi alters nothing in these appearances; on the other hand there is centripetal irritation of the vagi, which in the normal animal causes an increase in the number of the respiratory movements, although these become shallower, or it produces inspiratory paralysis, while in prussic acid poisoning it is entirely without effect. Prussic acid poisoning diminishes the normal oxidation processes in the animal body in two ways: 1st, by a diminution of the amount of oxygen absorbed and carbonic acid given off in the body; 2d,

by producing changes in the blood, the hæmoglobin of which gives off the oxygen which has been absorbed with greater difficulty. In this way the respiratory changes going on in the tissue cells are diminished, which, according to Hermann, gives rise to further manifestations of tetanoid spasm, while those remedies which are direct spinal cord irritants produce severe tetanus in frogs. Prussic acid tetanus, therefore, in warm-blooded animals cannot be due to an irritation of the spinal cord produced by prussic acid.

Whether the paralysis of the rest of the central nervous apparatus, the gray cerebral substance, and the spinal cord, which the loss of consciousness, voluntary power, and reflex irritability lead us to suppose exist, is due to the action of the prussic acid, or the interference with tissue respiration is doubtful. While direct contact with prussic acid rapidly paralyzes the sensitive and motor nerves, general poisoning results in death of the nervous centres at a time when the peripheral nerves are scarcely affected. Rapid prussic acid death, therefore, leaves the motor nerves and voluntary muscles excitable. In slow poisoning—that is, when death does not set in from smaller doses—the nervous paralysis spreads gradually from the centre to the periphery. (Kölliker.)

Circulation.—The complicated assertions of Preyer concerning the disturbances of the circulation produced by prussic acid have not been affirmed by the recent investigations of Böehm and Knie, Rossbach and Papilsky. The heart muscle and nerves withstand prussic acid longer than any other portion of the body. The vaso motor centre in the medulla is influenced much more intensely and rapidly.

In warm-blooded animals at the beginning of the effect the pulse becomes slower and the blood pressure is increased. But while the rapidity of the pulse varies later on, the blood pressure sinks after a few seconds far below the normal; this is the time when the venous blood begins to take on a bright red color; later on there is a second rise in blood pressure (during the convulsive stage) which continues until it has reached the zero mark. Even when the blood pressure is very much diminished the heart continues to beat quite forcibly; and even after the rest of the body is quite dead we can still observe that the heart continues to beat with a weak, wave-like motion. When the prussic acid, however, is directly injected into the blood the heart dies sooner than the rest of the body.

In cold-blooded animals there are at first diastolic intermissions, followed by increasing slowness of the heart's action, until finally death sets in.

Even in the extremest stage of poisoning, as long as the heart still beats the vagi are not paralyzed. Even when general death has taken place, as long as the heart continues to beat it can be brought to rest in diastole by irritation of the vagi. The vagi, however, are not in an irritated state, to which Preyer refers the slowing of the pulse; atropia neither hinders nor prevents the slowing of the pulse.

The primarily increased and subsequently decreased blood-pressure is due to primary irritation and secondary paralysis of the vaso-motor centers. The cause of the slowing of the pulse has not yet been positively ascertained.

Influence of prussic acid upon the temperature. The bright red composition of the venous blood led Hoppe Seyler to the conclusion that the normal oxidation process in the body is very much diminished, and, hence that the production of heat is diminished.

Wahl, however, found that the subcutaneous injection of aq. amygdal amar. resulted in an increase in temperature.

The more thorough experiments of Fleischer also showed that prussic acid does not act as an antiphlogistic remedy; for to produce this effect very large doses would be necessary, such as would be dangerous to life. It is true in sensitive animals there may be a great decrease, even from small doses, but such a decrease cannot be counted upon with any certainty.

Generally the inhalation of very highly diluted prussic acid gas does cause a slight lowering of the temperature; but in some cases the temperature remains constant in spite of twenty minutes' inhalation of the gas. If sufficiently large quantities are inhaled to cause tetanoid spasms then the temperature is temporarily increased, and post mortem a rise to beyond 40° is often seen.

Death from prussic acid is one of asphyxia, otherwise there is nothing characteristic except the odor and blood changes.

Therapeutic Application.—In our opinion prussic acid and its preparations can be very well dispensed with. They are of great physiological and toxicological interest, but of no great therapeutic value. They can well be replaced by other better and less dangerous agents.

The pathological conditions in which prussic acid preparations were used have been gradually narrowed down, until now they are only used symptomatically in some forms of cardialgia, and vomiting, to relieve cough and palpitation with præcordial anxiety. But, as we would expect, even these purposes are but poorly answered by prussic acid. In the small doses in which it can be used medicinally prussic acid acts as an irritant to various central organs (respiratory, vaso-motor, and motor centres); difficult and rapid breathing (convulsive expiration), increased blood-pressure, and convulsions; to decrease this irritability dangerous doses are necessary. Such doses are also necessary to diminish the irritability of peripheral, sensitive and motor nerves; apart from this the effect of small quantities of prussic acid is very evanescent, and hence would not be of much value, under any circumstances, in chronic pathological conditions.

Even if we would overlook our physiological knowledge, and judge from practical experience alone, we would say that, whenever we have used prussic acid alone without morphia or atropia in the above-mentioned conditions, we were unable to observe any marked influence over the pathological state; we therefore consider it best not to use a preparation which is of no evident utility while it is too dangerous for the "ut aliquid fieri videatur" indication.

To satisfy those physicians who wish to use the drug, we will say that it is used in the cardialgias, which are not connected with any pathological condition, but are only symptomatic, and which generally occur in anæmic or nervous individuals. Prussic acid is given in the dry convulsive cough. Some observers have found it useful in some cases of whooping cough, while they found it useless in others. Prussic acid preparations are used in heart affections when these are accompanied by great præcordial anxiety or pain (angina pectoris). But it should not be given to relieve a severe attack of the latter affection.

Externally, as a pain alleviator, prussic acid has no advantages over other narcotics.

Dosage and Preparations.—1. Hydrocyanic acid—acid hydrocyan-

icum—from 0.0005—0.005 in alcoholic solution. A dangerous preparation; best not to use it at all.

2. Aqua amygdalarum amarum concentrata—bitter almond water—1 part of prussic acid to 1000 of fluid, is a colorless or somewhat opaque fluid. Most frequently used of all the preparations—dose, 10–40 drops (ad 2.0 pro dosi; ad 7.0 pro die.)

3. Aqua am. am. diluta—known as cherry water, because it is used instead of ag. cerasor. nigr.—contains one part of aq. am. am. concentrated to 19 parts of water from 10.0—50.0 pro dosi (100.0 pro die).

4. Aqua laurocerasi—cherry laurel water, prepared from the folia lauro cerasi—dose and strength like that of aq. am. conc., which can be substituted for it.

5. Amygdalæ amaræ—semen amygdali amarum, from amydalus amara; bitter almonds contain in addition to other constituents like that of sweet almonds a nitrogenous glucoside amygdalin, which is extracted, after the oil, by alcohol. It is when crystallized odorless, slightly bitter, and readily soluble in boiling water and alcohol. Under its own form it is not poisonous, but when brought in contact with emulsin, a ferment contained in the almond, it is decomposed under favorable conditions into prussic acid and an ethereal oil of bitter almonds. Bitter almonds taken in large quantities might therefore be injurious and even fatal to animals and men. They are not used therapeutically.

6. Folia laurocerasi—used pharmaceutically for the preparations of aqua laurocerasi.

Treatment of prussic acid poisoning. A number of antidotes have been recommended, but the rapidity with which the poison acts renders any antidote useless; apart from this their utility has not been proved experimentally. Such are ammonia, ether, hydrated oxide of iron, with magnesia. We have already spoken of the real utility of atropia injections to improve the action of the heart.

When the poisoning is not too rapid, cold douches (in warm baths) to the head and upper part of the body, and the application of cutaneous irritants, and, hypodermatic injections of camphor, have been shown to be useful. If the respiration stops, it must be restored by artificial means. Preyer has by this means restored animals in whom the respiration had ceased; the conjunctivæ were no longer sensitive, the pupils extraordinarily dilated, and the eye-ball protruded. A necessary condition, however, is that the heart should still be beating.

THE ALKALOIDS.

Even in the most poisonous of plants the poisonous principle is a basic body, bound to one or more acids, and which is known as a vegetable base or alkaloid.

All of these are, without exception, nitrogenous bodies, and form salts with acids. A few (nicotin, spartein, and coniin) are fluid, free from oxygen, and can be distilled. Most free alkaloids are not soluble in water, but soluble in alcohol, ether, and chloroform. Their salts are readily sol-

uble in water; all have a strong alkaline reaction and a bitter taste.

The chemical constitution of the various alkaloids is entirely unknown; of most we know only the empirical formulæ, while only in recent times have they been at all studied.

The importance of the alkaloid to the plants themselves we do not know; we know only that botanically identical plants contain a variable amount of the alkaloid depending on the soil, climate, and season. Thus similar plants will vary in their poisonous power.

Upon the animal body the alkaloids have an intense effect. Now intensely poisonous, again highly curative, varying with the quantity as well as the kind of the alkaloid.

Most of these have a powerful influence upon the nervous system; and, indeed, different alkaloids upon different portions of the same. A few, like veratrin, exert also a local effect upon the skin and mucous membranes.

It was for a long time entirely unknown how the alkaloids exert their powerful effects in such small doses; how they affect the organic substrata; mysterious and unknown powers were ascribed to them.

Schmiedeberg believes that in consideration of the very small quantity of digitalin, for instance, which is sufficient to poison the frog's heart ($\frac{1}{2000}$ milligr.). The poison does not cause a chemical change or alteration of the contractile substance, but that the cause of the altered properties of the muscle is a change in its molecular constitution. We can readily believe that the normal molecular constitution of materials that go to make up the muscular fibres (water, salts, protoplasms, etc.) must be maintained intact if the muscle is to perform its functions; this molecular balance is disturbed by the addition of the small quantities of digitalin. But we do not see, nor does Schmiedeberg explain, how this very small quantity can produce such extensive effects, nor do we think it any easier to understand it by supposing a physical molecular change rather than a chemical one in the constitution of the affected organ. What forces, indeed, retain these minute quantities for so long a time in contact with these muscles and nerve cells?

Starting from the well-known fact that quinine solutions lose their fluorescence when in contact with albumen, we (Rossbach) subjected egg, muscle, and serum albumen to the action of various alkaloids, and found that albuminous

solutions, when brought in contact with an alkaloid in a warm atmosphere, were converted into a more coagulable and less soluble compound; furthermore such albumen loses its affinity for oxygen, and is no longer peptonized by it or by gastric or pancreatic juice. In the living animal, also, we were able to show a change in the solubility of much albuminate after poisoning with veratrin.

We have therefore collected a number of facts, some the result of our own investigation, and some that of others, all of which indicate that the alkaloid produces a chemical alteration in the living cell, which results in a depression and complete arrest of the oxidation process going on in the cell. We therefore believe that the alkaloids affect the organism in a manner similar to that of other chemical poisons (alkalies, metals, and acids); they differ from these only in the degree and manner of their affinity. The alkalies, metals, and acids do not so readily act as poisons to the general system because their affinity is first satisfied by the superficial tissues (skin and mucous membranes) by which they are bound, or because they are too rapidly excreted from the body. Were it possible during life to bring caustic potassa or sulphuric acid in contact with the great nervous centres, the effect (upon the general system) would be at least as well marked as that resulting from the alkaloids. The small doses of the alkaloid, not being bound anywhere else, come to the nervous system with their affinity still fresh; thus most of a hypodermatic injection of morphia reaches the brain, although none of a hypodermatic injection of sulphuric acid ever reaches the general nervous system; it enters into combination at the place where it is injected.

Again it needs but very little of a foreign substance to excite the nervous system, for even in conditions of greatest irritability the chemical alterations of structure in the brain are infinitesimal. The amount of cold produced by the evaporation of a drop of a concentrated sodium chloride solution from a bare nerve trunk, or a trace of some acid applied to the same, causes a great change in function; so also a mere trace of chemical alteration produced by an alkaloid would result in great functional disturbances; to produce this only traces of alkaloids are necessary. We can thus readily conceive that a decimilligram of some alkaloid will cause important disturbances of nerve function.

We should not be confused in our study by the great va-

riety of effects produced by the alkaloids upon the nervous system; when analyzed these effects are after all only of two kinds—those of irritation (excitement) and those of paralysis. The rest is not the effect of the drug itself, but is owing to the fact that the various nerves react to irritants according to their own specific fashion; in the eye there is a sensation of color, in the tongue of taste, in the nerves of sensation, touch, or pain, in the motor nerves the irritation results in muscular contraction.

It is not necessary to imagine that every individual agens exerts a peculiar influence upon the nerves. The method of action of small quantities of alkaloids may be exactly similar to that of evaporation on a nerve trunk.

Different alkaloids have individual affinities for different organs, and this is a further reason why alkaloids, even in minimum doses, exert such powerful effects upon individual organs.

The fact that we only observe disturbances of the nervous system, and rarely in the remaining cell systems of the body, would be accounted for either on the ground that all of the alkaloid is absorbed by the nerve cells, or perhaps that our methods of examination are not sufficiently precise to reveal disturbances of functions of other organs. The reason why alkaloids should affect various organs in various ways would be found in a cause similar to that which produces only a molecular disturbance of the particles of a heavy body when acted upon by a force sufficient to move a lighter body.

Tolerance.—For a large number of the alkaloids Rossbach has shown a tolerance of the organism for increasing doses. This tolerance sets in very rapidly, but not all organs become accustomed to these doses in like manner. Some always react in a similar manner, while others soon become insensible to the action of the drug. This tolerance, however, has a limit, beyond which the poison is not borne without a bad effect. The enormous doses produce poisonous effects similar to those of the primary small doses, while the continued use of small doses influences many more organs than before. The organism is only maintained in good health after tolerance for the drug has been established by the continued administration of small doses; without the drug there is felt a sensation of *illness, even* real symptoms of disease, together with a con*stant longing for the* drug, will be manifested. The

causes of these remarkable facts are probably many. Some observations would seem to show that as the patient becomes more tolerant of the poison, its influence is exerted upon more organs, and thus the same quantity becomes more divided, so that less falls to the share of each individual organ. Again, after long-continued use, the poison is more readily excreted by all the organs of the body, and thus does not accumulate in these organs as before.

Antagonism.—For a long time it has been believed that many alkaloids, such as atropin, pilocarpin and physostigmine, have the power of antagonizing each other's effects upon the various organs, so that when life is endangered by one alkaloid, it can be saved by the action of another. Our (Rossbach) investigations have led us to the following conclusions:

1. There is no true two-sided physiological antagonism between the action of two poisons, either upon individual organs or upon life.

2. When a poison in certain doses exerts upon any organ a physiological action exactly contrary to that of another poison upon the same organ, the one having a paralyzing, the other an irritant action, the paralyzer does antagonize the irritant, but only as far as that particular organ is concerned, and even here it results not in a restitution to healthy physiological function, but merely substitutes for the healthy function a pathological one upon which the other poison is powerless.

3. A poison which is an irritant to a limited part of an organ never suspends the action of a preceding paralyzer. It is true such an effect may be simulated because a paralyzing poison may have only paralyzed the terminal nerve fibres of an organ, while it leaves intact the more central cells or muscular portions; if an irritant acts upon the latter it might give rise to the appearance of having effected a reawakening of the paralyzed portions.

4. We can therefore only imagine one case in which life could be saved by the effects of antagonizing the action of one poison by another, and that is when a powerful irritant endangers life by an almost fatal irritation of some organ which is necessary to life. In this case life might be spared in one of two ways: either by reducing the irritability of the excited organ by a paralyzer, or by paralyzing the organ itself; in the latter case we must be careful to avoid the other *extreme* of poisoning the patient by the paralyzer.

5. This paralyzing poison must be administered, therefore, in gradual doses, until sufficient has been given to produce the desired effect, and no more. In this sense, then, we can speak of a partial antagonism between the effects of two drugs.

6. When two poisons have an antagonistic effect upon one organ, it does not follow that this antagonism is exerted upon any other organs at the same time.

Since the alkaloids have no especial affinity for the skin, mucous membranes, or blood, the same effects are produced whether these be injected under the skin or directly into the blood; in this respect there is a great difference from the alkalies, metals, acids, and aromatic compounds.

Schiff has found that alkaloids like morphine, nicotine, and hyoscyamin have less effect if they are made to traverse the portal vein before they reach the general circulation. This observation appears to be confirmed by the experiments of Heger, who found that when several organs were artificially injected with solutions containing alkaloids, the muscles and liver retained these to a greater extent than any other organs.

THE ALKALOIDS OF CINCHONA BARK.

Quinine, chinonine, quinidin, cinchonidin, cinchona barks of the species cinchona, and family rubiaceen, grow in South America, and are also cultivated in many other tropical countries. We can distinguish three varieties in color and in the percentage of alkaloids which they contain. These are:

1. Yellow calisaya or cinchona bark (cortex chinæ calisayæ) contains from 2 to 3 per cent of quinine and .4 per cent of cinchonine.

2. Red cinchona bark (cortex chinæ ruber) contains at most 1 per cent of quinine and .4 per cent of cinchonine.

3. The gray or brown cinchona bark (cortex chinæ fuscus) contains at least .8 per cent quinine and 1–2 per cent of cinchonine.

The alkaloids are extracted from the powdered bark by diluted acids, from which filtered solutions they are precipitated by soda, and again from this precipitant they are extracted by boiling alcohol.

The following, according to O. Hesse, are the chief constituents of quinine bark:

1. Quinine, $C_{20}H_{24}N_2O_2$, precipitated from its solution in dilute acids, by an excess of ammonia; this alkaloid is amorphous, free from water, but becomes crystalline as soon as it absorbs $3H_2O$. The anhydride is also deposited in small white needles, when the slightly warmed solution of a quinine salt is precipitated with soda or sodium bicarbonate. A portion of the anhydride is soluble at 15° in 1960 parts of water, and a portion of the trihydrate in 1670 parts. Quinine solutions (with dilute sulphuric acid) have the property of fluorescence; hydrochloric acid, metallic chlorides and other substances prevent this fluorescence, hence

the fluorescope is not a positive test for quinine. Quinine is a strong base, which decomposes the salts of ammonia, and forms, with from 1 to 2 equivalents of acid, neutral and acid salts.

2. Cinchonine, isomeric with quinine.

3. Dichonquinine, $C_{40}H_{46}N_4O_2$. is amorphous and forms amorphous salts. It forms the greater part of the so-called chinoidin.

4. Cinchonidin, $C_{19}H_{24}N_2O$.

5. Cinchonin, isomeric with 4.

6. Dicinchonin, $C_{40}H_{48}N_4O_2$. We have also homocinchonidin, homocinchonin, dihomocinchonin, chinamin $C_{19}H_{24}N_2O_2$, conchinamin, paricin, $C_{16}H_{18}N_2O_1$, paytin $C_{21}H_{20}N_2O+H_2O$, paytamin, cuscomin, $C_{23}H_{26}N_2O_4+2H_2O$, aricin, isomeric with the foregoing and cuscomidin.

Besides these there are chinovin, $C_{30}H_{48}O_8$, a bitter glucoside, which is decomposed when heated into a mannite like body and kinovic acid, $C_{24}H_{38}O_4$, the latter of which is found in the bark. Kinic acid, $C_7H_{12}O_6$, found chiefly in the cinchona bark intimately associated with the quinine; also found in coffee beans and other plants. In the urine it reappears as hippuric acid. Kinotannic acid, of which the bark contains from 1–3 per cent.

Since all of the cinchona alkaloids enumerated above are very similar in their effects; furthermore since cinchona bark acts principally like its alkaloids, except that on account of the tannic acid it disturbs digestion, and finally since quinine is the most powerful of all the alkaloids, it follows that all other cinchona alkaloids, as well as the bark, are therapeutically superfluous. For these reasons we shall only consider the action of the quinine alone, giving the dosage, however, of the other preparations also.

QUININE.

Since pure quinine is insoluble in water it is used principally in the forms of the muriate and sulphate.

According to Binz the best preparation to use is the muriate, because it contains 8–9 per cent more of the base than sulphate. It has the advantages of being more soluble and absorbable, and of keeping better than the sulphate.

When quinine is given drugs and preparations containing tannic acid must be avoided, for the quinine tannate is most insoluble of all preparations.

PHYSIOLOGICAL ACTION.

In its antifermentative and antiseptic power, and its effect upon the healthy and diseased organism, quinine has shown such an extraordinary resemblance to the aromatic compounds, especially salicylic acid, that we cannot help suspecting the presence of a benzol radicle in its composition.

These effects have been so thoroughly discussed under phenol and salicylic acid that we can here treat this portion of the subject much more briefly.

Upon decomposition quinine exerts, especially in a neu-

tral solution of 0.2 per cent, a preventive action; a similar effect is produced upon fermentation which is the result of the action of organized ferments; thus, for example, upon alcoholic, lactic, and butyric acid fermentation. On the other hand, according to Binz, it has no effect upon the action of emulsin upon amygdalin (the formation of prussic acid), and the conversion of starch into sugar.

This antifermentative and antiseptic power is probably due to a fatal influence which quinine exercises over the lowest organisms, such as the bacteria, vibriones and yeast cells.

Quinine exerts a much more powerful effect upon these organisms and the infusoria than upon the larger animals.

In the former death results, which resembles that caused by the deprivation of oxygen. Atropia and morphia, although much more poisonous to the higher organisms than quinine is, have a less fatal effect upon the lower organisms than the latter drug.

Some of the lower organisms, however, flourish very well in quinine solutions (Binz). Such are salt-water amœbœ. We have already shown that all of these effects both upon the lower organisms and decomposition processes are due to positive alteration in the albuminoid bodies produced under the influence of quinine (Rossbach).

DISPOSITION AND ACTION OF QUININE UPON THE ORGANISMS OF THE HIGHER ANIMALS.

Disposition of Quinine in the Organism.—Quinine is not absorbed by the unbroken skin, but is absorbed by mucous membranes, through subcutaneous injection, and by wounded surfaces. The solubility and hence the absorbability of quinine solutions is very much increased by the muriatic and lactic acid of the gastric juice. (The sulphate is much less soluble and absorbable than these salts and should not therefore be as much used in practice.) A large, if not the largest, portion of the quinine is absorbed by the stomach.

In the intestine the alkaline intestinal and pancreatic juice would very much diminish the solubility of the quinine salts, did not the carbonic acid gas present in the intestine neutralize the effect to a slight extent.

The acids of the biliary salts form the most insoluble *compounds with quinine*, and it is only when these are de-

composed by carbonic acid gas, or when there is an excess of bile, that the latter can be absorbed (Kerner).

Most of the quinine, however, is absorbed into the blood, and in the fæces there is no longer any trace of quinine, except where the preparation used was very insoluble (Kerner).

The quinine is excreted by all the excretions, especially by the urine. In the latter it reappears in the course of ten minutes after its absorption, and is almost entirely out of the body in the course of twelve hours. But even after 48–60 hours a trace of quinine can still be found in the urine (Kerner).

The largest portion of the absorbed alkaloids is found in the urine in the form of an amorphous modification, a small part as a crystalline substance, which Kerner calls the dihydroxyl quinine, $C_{20}H_{26}N_2O_4+4H_2O$, i. e., quinine in which 2(HO) have entered. This is so called because of its resemblance to an oxidation product obtained from potash permanganate. It is entirely indifferent in its action upon the lower and higher animals (Kerner). According to Personne quinine is for the most part again changed into resinous substances.

Digestive Organs.—Quinine is intensely bitter even in the strength of 1:10000. The bitter taste remains for some time, and cannot be removed by rinsing the mouth with water. It is therefore probable that it produces quite a permanent alteration in the terminations of the nerves of taste. As a reflex result there is increased salivation; a further effect upon the salivary glands is not seen. When quinine solutions are injected into Wharton's duct the secretory filaments of the chorda tympani become paralyzed while the vaso-motor (dilating) filaments of the same nerve, as well as the secretory filaments of the sympathetic, retain their irritability. For the paralysis of the latter much larger doses are necessary (Heidenbain).

After small doses (0.01 to 0.05 grm.) we find no prominent gastric symptoms. An increase in the secretion of the gastric juice has hitherto not been observed by any one, nor would it appear at all probable, according to Buchheim, that such an effect is produced. The frequent assertion that the constant administration of quinine results in increased appetite does not appear to be well founded. It is true that *when* febrile diseases are cured by quinine *the appetite is improved*, but this is the result of the im-

provement in the disease, and not directly of the quinine. Buchheim and Engel have found that the presence of quinine in the stomach of the living animal retards digestion.

The gastric juice of the dog, which contains 0.0002 per cent of quinine, digests one tenth less albumen than pure gastric juice (Rossbach and Goldstein). We must therefore deny that small doses of quinine improve digestion and appetite; on the contrary, in many persons it causes nausea, vomiting, and a feeling of sickness in the stomach.

Large doses (0.3 to 2.0 grms.) may even cause vomiting, and symptoms of gastric irritation, especially when we use the sulphate and not the muriate. In febrile diseases these gastric disturbances are more frequent and more severe.

The biliary excretion is not increased by quinine (Buchheim and Engel). On the other hand we cannot decide that there is any diminution, which the contracted spleen would lead us to expect.

We do not know that it has any effect upon the remaining intestinal juices or upon the intestinal movements.

Blood and Organs of Circulation.—Quinine causes the oxygen to be more firmly bound to the hæmoglobin, and as a result this gas is longer retained (Bonwetsch, Binz, and Rossbach). The addition of small quantities of quinine retards the energetic formation of acids, which takes place in fresh blood under the influence of the air and the action of the red blood globules (Zuntz). Quinine weakens the ozone reaction which is obtained when guaiac paper is dipped into the blood. This it does whether the quinine be introduced into the living blood, or when the latter has been drawn from the body (A. Schmidt, Binz). When large doses of quinine are given the red-blood globules become enlarged, because of the larger amounts of oxygen which they hold in combination.

Small doses of neutral quinine solutions paralyze the white-blood globules, and cause them to loose their amœboid movements. Large doses ($\frac{1}{2000}$ of the bodily weight) of quinine will diminish the number of these globules in the blood to one fourth in the course of a few hours. In cold-blooded animals quinine prevents the migration of the white blood corpuscles (and hence the formation of pus) from the blood vessels when given in large doses ($\frac{1}{1000}$ of bodily weight), the heart's action *remains normal*; and therefore this effect must be due *to the paralysis* of the corpuscles themselves (Binz and

Scharrenbroich). Zahn and Koehler, however, consider this effect the result of simultaneous weakness of the heart.

In the omnivora quinine causes the spleen to be contracted (Piorry, Küchenmeister, Mosler, and Landois). This is also found even when the nerves have been previously severed. Whether this is the result of a contraction of the contractile elements produced by irritation of the splenic nerves, or whether it is due to an interference in the cellular hyperplasia, we do not know.

Quinine has not so marked an effect upon the circulatory organs as the special circulatory poisons; the following are the most reliable observations which we have concerning this point.

After small and medium (divided) doses of quinine (up to 1.0 grm.) Schlokow, Blockmeissner, and Jerusalimsky observed an increase in the heart's action and blood pressure. Jerusalimsky saw the same in women after 0.3 to 0.6 grm. doses. The latter observer accounted for this by supposing that quinine acted as a paralyzer of the imbibitory apparatus of the heart, and an irritant to the motor apparatus of the heart. Binz, however, denies that such doses can have any effect upon the vagus nerve, and therefore these results must be due to the latter cause. Eulenberg has found that in frogs the heart beats more slowly and feebly even after small doses.

On the other hand, most observers (Briquet, Dumeril, Reil, Schlokow, Lewitzky, Schroff, Jr., and Liebermeister) affirm that large doses of quinine (1.5 to 2.0 grms.) cause both in healthy and febrile persons a slowing and weakening of the heart's action. Jerusalimsky found that in many healthy animals (dogs) the pulse was increased even under large doses, and that this increase continued when the dose was repeated until the heart ceases beating. We must however consider this as an exception to the general rule, for we are positive that in fever patients the pulse does sink under the action of quinine; whether this should be looked upon as the direct result of the lowered temperature or the influence of the quinine upon the heart is immaterial.

This slowing of the heart's action under quinine is not due to irritation of the vagi, for it occurs even when these nerves have been cut, apart from the fact that under these circumstances the vagus is not very sensitive even to the electric current; it is much more probable that this effect is due to the diminution of the irritability of the motor

nerves of the heart, and to weakness of the heart muscle (Lewitzky, Eulenberg, Schlokow, etc.). The diminished blood pressure is partly due to this weakness of the heart, and partly to dilatation of the peripheral arteries from paralysis of the vaso-motor centre and vasor nerves. (V. Schroff, Jr., and Heubach); the latter would seem to be proved by the fact that the blood pressure is not increased even under severe sensitive irritation.

Enormously large doses given internally paralyze the vagus after hours have passed, without, however, increasing the rapidity of the previously paralyzed pulse. Soon the gradually diminishing pulsations of the heart cease in diastole, and the heart fails to react even upon direct irritation.

Paralysis of the heart follows paralysis of respiration (Binz, Heubach); it is only when enormously large doses have been injected into the jugular vein through the heart that paralysis of the heart instantly takes place, so that the animals die from cerebral anæmia and the want of oxygen, which is the result of convulsions.

The bodily temperature is only slightly altered in healthy animals and men. We have, it is true, no positive investigations on this subject, but from all accounts it would appear that the temperature is not even lowered to the extent of $\frac{1}{10}$ of a degree. Liebermeister saw no change follow doses of 2.0 grm. given in divided doses in the course of 6 hours. After 2.5 grm. the temperature rose to the extent of 0.1° C. Sydney Ringer saw the temperature fall after 1.25 grm. to a similar extent. Jerusalimsky saw a very slight fall from small and large doses; several times, however, there was a rise to the extent of 0.7° C. In healthy people the administration of large doses, not sufficient to effect sensation of the pulse, has the tendency to allow the temperature to run its normal course; it is less raised by work, and sinks more rapidly after work has been done. In this manner quinine diminishes sweating after work upon a hot summer day (Liebermeister and Koerner).

It is highly probable that the healthy organism is very much cooled by large doses of quinine.

As to the effect of quinine upon the temperature of fever patients, we find many contradictory assertions, even among equally reliable obserqers.

It is positive, however, that quinine can reduce the temperature from 1–3° C. in a large majority of certain con-

tinued febrile diseases; in certain other fevers, however, no favorable effect has been seen to follow the use of quinine. In consideration of the importance of this question, it is desirable to study these various cases more accurately.

In animals suffering from septicæmia after injections of pus into the blood, Binz and Manassein obtained favorable results from the use of quinine; life being prolonged and sometimes even saved by its use. It is true, the doses used by Manassein were almost large enough to cause death of themselves. Popow, on the other hand, was unable by its aid to preserve life or to increase the number of recoveries from the effects of purulent injection into the blood. In the surgical septicæmia of human patients Socin was very successful, but only after enormous doses (6–7.0 grm. daily), given (with wine) for a long time. Hüter also confirms the antipyretic action of large doses, but has never seen quinine cure a single case. Our impartial opinion must hold, that in septicæmia quinine is not of very great utility, and is best replaced by alcohol.

In traumatic erysipelas Socin did not see any decline in temperature result from the use of quinine, while large quantities of alcohol did produce this effect. Busch, who confirmed these observations, found that this lowered temperature, which is the result of alcohol, is only very temporary, but can be rendered more permanent by a subsequent quinine treatment.

In articular rheumatism, according to Liebermeister, the utility of quinine is very slight.

All observers agree that quinine is useless in relapsing fever.

In the exanthematic fevers, such as variola, etc., Schullert, Steiner, Ladendorf give favorable reports; Maudeville and Popow unfavorable ones. Slight puerperal fever, without any evident localization, where there is no centre of infection, gives way to quinine treatment, while serious cases do not (Conrad).

According to Jürgensen, doses up to 5.0 grms. have a very powerful antipyretic action in croupous pneumonia, but we were never able to observe that quinine ever arrested the pneumonic process.

In typhus, Liebermeister, in an experience of 600 cases, found that large doses lowered the temperature in some, but not in all; this lowering was greatest when it occurred simultaneously with a spontaneous remission; that after

night-doses lower in the morning than in the evening after day-doses.

There is but one opinion concerning the favorable effect of quinine in intermittent.

In continued fevers, the antipyretic action, when it occurs, lasts until the quinine has passed out of the system; that is, on an average of from 12 to 24 hours (Thau). The average antipyretic dose in adults is from 1.0 to 2.0 grms. Under 1.0 grm. no especial lowering of the temperature is observed; divided doses, although large in the aggregate, have not a powerful effect.

Quinine, then, is an antipyretic in many but not all fevers; the fact that even in those where it does so act it does not always succeed in the most serious cases, should not surprise us. There are fires so great that even water cannot quench them; the same may hold true of quinine in those very bad cases, and yet because quinine does not succeed in these, some observers deny it any antipyretic power.

Nervous System.—In cold-blooded animals (frogs) the following facts have been observed: Small doses of amorphous quinine muriate (0.001–0.005 grms.) have an exalting action upon reflex irritability; larger doses, on the other hand, a depressing effect, partly due to a depressing action upon the heart's action, partly to a direct paralysis of the spinal ganglia. Even in frogs under the influence of strychnia the reflexes are almost entirely suspended under the influence of quinine.

Chaperon thinks this paralysis is due to an excitation of the reflex and inhibitory cerebral centres, but apart from the doubtful existence of these (Setschenow, Binz, and Heubach) experiments lead to directly contrary results. The voluntary motions are only suspended by very large doses of quinine. The peripheral nerves, both motor and sensitive, are not much altered in cases of quinine poisoning, but if motor nerves are placed directly in quinine solutions, their irritability is at first exalted, but later on quickly diminished, until entirely abolished, as compared with another nerve placed in a sodium chloride solution (Heubach.)

In warm-blooded animals, especially in man, the following disturbances of the nervous system are observable, which are the direct result of the quinine upon the nervous system, and not secondary to the gastric catarrh, nausea, *vomiting, etc.* From doses of 1.0 to 2.0 grm. there is at

first a feeling of well-being, followed by diminished sensibility, ringing in the ears (compare salicylic acid) and fulness of the head. The latter increases until we have confusion of ideas, headache, dizziness and a pulsating sensation in the carotids (quinine intoxication). The ringing in the ears becomes stronger, certain hallucinations of hearing set in, and the acuteness of hearing is diminished. The sight is dimmed and the field of vision darkened; the pupils are somewhat dilated. Finally indifference, drowsiness, and great weariness set in. When no more quinine is taken these subjective sensations disappear after a few hours. The ringing in the ears and headache last longest. When the above doses are continued, or one large dose of 2.0 to 4.0 is given, the symptoms become more serious. The walk become shaking and ataxic; delirium sets in; complete deafness and sometimes even amaurosis begin to appear; the speech is disturbed. These symptoms disappear, generally, although the deafness and disturbed vision have been known to last for years.

Doses larger than 4.0 grm. may produce death, accompanied by convulsions, general paralysis, and sudden collapse (observed in men, dogs, and cats).

The quinine intoxication is most probably due to a direct alteration of the cerebral ganglia, and is not the result of a diminished blood pressure.

The drowsiness is independent of the bodily temperature, both in healthy and sick people, and, according to Binz, it can be given instead of morphine and chloral.

The disturbances in hearing and sight are due to a direct influence upon the nervous apparatus of these senses.

The diminished sensitiveness, the apathy, etc., must be considered, at least in cold and warm-blooded animals, less the result of a change in the peripheral, sensitive, and motor nerves, than a diminution of the conductivity of the sensitive and motor paths in the spinal cord; in favor of this view we may consider the observation of Schroff, Jr., that the vascular reflex to sensible cutaneous irritation is diminished.

Respiration.—In warm-blooded animals the respiration is unchanged after small doses, but medium doses accelerate it (Strassburg, v. Boeck). Very large doses render it fatally slow; *all these changes* are probably due to an affection and paralysis of the respiratory centre of the medulla.

The over-filled capillary circulation and the pulmonary hemorrhage are probably due to cardiac disturbances.

Voluntary Muscles.—The muscle-curve of cold-blooded "quininized" animals is twice as long as that of the normal voluntary muscles (Buchheim).

Tissue Metamorphosis.—According to experiments of Kerner upon himself, small doses of quinine cause a diminution of the amount of nitrogen excreted in the urine. After a single daily dose of 1.0–2.5 grm. it is diminished by 24 per cent. So also the sulphuric acid of the urine by 39 per cent, while on the other hand the water of the urine is somewhat increased. Since, in the experiments of Kerner, severe gastric and general symptoms of poisoning set in, and the amount of nitrogen contained in the food was not computed, v. Boeck experimented with non-poisonous doses of quinine upon dogs, taking every precaution of Voit's school, and yet found a diminution in the decomposition of albumen. During the five days that the quinine was used, there were only 10.0 grm. less of nitrogen excreted than was present in the food. More remarkable, however, is the fact that both Bauer and Künsth found that when the temperature is diminished by quinine, sodium salicylate and cold, there is a regular but slight diminution in the amount of nitrogen excreted in the urine.

Interchange of Gases.—Boeck and Bauer found in cats and dogs that small doses of quinine diminish the excretion of carbonic acid, and the absorption of oxygen. Since the diminution in the quantity of carbonic acid excreted (by 9 per cent) about equals the diminution in the decomposition of albumen (by 11 per cent), it is probable that the former is the result of the latter. One could not decide positively, however, that the decomposition of the non-nitrogenous matters was not also affected. It is positive that diminution in the quantity of CO_2 excreted is not due to a diminished absorption of oxygen; von Boeck and Bauer are in like manner convinced that quinine reduces the excretion of carbonic acid and the reduction of oxygen in man as long as restlessness and increased muscular activity do not occur. In animals, also, a reversal of conditions prevails when greater restlessness and stronger muscular and more rapid respiratory action supervene, there being an increase in excretion of carbonic acid and consumption of oxygen. *The capacity of* the cells for oxidation is not so greatly

affected by quinine, that it is not raised above the normal by opposing influences.

That Binz-Strassburg noticed in rabbits no change in carbonic acid excretion, either with or without fever, was probably due to the selection of the animal and the abnormal conditions present during the experiment (the animal was tracheotomized).

Excretion.—Perspiration during the summer is checked in workingmen, while the urine, at least in healthy persons, is increased (Kerner).

THEORY OF THE ACTION OF QUININE.

All investigations which have been made regarding the action of quinine on the organic substrata and the simple processes of the animal body—namely, on the albumen (Rossbach), on the processes of decomposition and fermentation (Binz and Schueler), on the lower organisms (Binz, Rossbach), on tissue metamorphosis (Kerner, Von Boeck and Bauer,) on the blood (A. Schmid, Bonwetsch, Zuntz, Binz, Rossbach), tend to one conclusion concerning the operation of quinine, namely, that, by its union with the albumen of the cells they are made less susceptible to the influence of oxygen, and are, therefore, not so easily oxidized. The fact that in the process of fermentation (which depends upon causes very similar to decomposition in living bodies), quinine promotes the whole process, and when introduced into living organisms checks the decomposition of albumen, depends upon a quantitative distinction (Von Boeck). In order to increase the decomposition of albumen in the living organism, greater quantities of quinine are necessary. This is clearly proven by Kerner's experiments upon himself; after large doses of quinine symptoms of poisoning appeared, and at the same time the excretion of carbonic oxide fell to a marked degree. The fact that a number of the functions of the higher animals are quickened by small quantities of quinine does not affect the fundamental principle, for every sudden diminution in the tissue metamorphosis in the cells (for instance, a sudden loss of blood) is at first responded to by functional quickening of the organs.

The cause of the decrease in temperature is the subject of *great strife of opinion.* A decision is not now attainable, *yet we may outline* the present aspect of the question as

follows: Since decrease in temperature occurs in animals with fever, and which are enveloped in wadding, and increase in radiation of heat from the body of these animals is hindered; since, also, the temperature rises after severing the cervical spinal cord, owing to the retention of heat in the body, which is hindered from radiation during the continuation of these processes; since, also, on decapitation, every indirect action of the circulation and the nervous system is prevented by death, there is nothing for us but to regard the influence of quinine in lowering the temperature as affecting the heat-producing processes in the organism, this influence being the result, in part, of the previous chemical condition of the cells (Briquet, Liebermeister, Hannyn and Quincke, Binz). This opinion is made more probable by the decrease in the consumption of oxygen (*q. v.*).

In our present state of knowledge it seems premature to refer to the power of influencing the nerve centres that govern the elevation and reduction of temperature.

Nervous influences act in part against and in part in support of this fundamental action. As quinine acts first on the central nervous organs, a great number of muscular cells are excited, and consequently muscular activity is increased by the accelerated pulse, the more rapid circulation, the quicker breathing, the increased tissue-metamorphosis and higher temperature. But this is true only so long as the quinine acts directly on a very small cell territory. We can thus clearly see why healthy persons show no reduction of temperature, or very little. When a sufficient quantity of quinine is administered to permeate the largest part of all the cells of the body, a number of functions are so changed (we refer only to the decrease in the pressure of the blood, and the increased inactivity of the muscles) that the fundamental influence of quinine on the cells becomes even stronger and more confirmed.

Fever temperature may be regarded as being produced, aside from the influence of this agent, by another factor, as for instance in malaria. "The cause of malaria may be a low organism, which comes periodically from its place of generation in the lymphatics or the spleen, at each time bringing with it the phenomena of fever; or it may be a poison held in chemical solution, which periodically requires decomposition of animal tissue and a high degree of animal heat. We must consider, however, that in the nor-

mal human organism these various conditions must prevail, which would render such a poison harmless, such as, no doubt, cause the spontaneous breaking up of miasmatic diseases. If these innate recuperative powers are assisted by the influence of an antidote circulating through the system, the action of the poison in solution ought to be comparatively powerless for continued injury; yet, instead of ceasing in a few minutes, the fever continues for hours." (Binz.)

We have shown under the aromatics how far we are from being able to scientifically prove this hypothesis; but it would be wrong not to recognize that, in the present condition of science, no better hypothesis can readily be advanced. We may assert, however, that, the operation of quinine to diminish fever, in part by destroying the fever-producing cause, affords an explanation for two very hard facts: first, that it acts only in feverish conditions, and second, that only in certain fevers it has a strong effect in reducing heat. The causes of fever are of very different kinds, and many may assist the action of the quinine, while many others hinder it. An example is found in Obermeier's Recurrens-Spirilles; according to Engel, a one half per cent solution of quinine had no injurious effect; so also phenol, hypermanganate of potash. On the other hand, mercury salts in solution, though in proportion 1:3000 to 1:4000 were destructive, and glycerine also proved very harmful. We could show the notorious unreliability of quinine in recurrent fever to better illustrate its want of influence on the recurrens-spirilles. On the other hand, intermittent fever is strongly affected by quinine, and typhus poison is moderately affected. It is now comprehensible why articular rheumatism could not be cured by quinine, but required salicylic acid, why in some diseases large, in other medium doses reduce temperature, etc.

It is clear that the decrease in temperature has further consequences, which are not to be ascribed to the action of quinine as such, but only in part to its good effects. The accelerated pulse, as far as it was due to high temperature, had to fall with lower temperature. We must guard ourselves against attributing the whole of the action of the heart to the effects of quinine. With the passing off of the fever-temperature, the general condition is bound to improve, as in typhus patients, for instance, the numbness of the sensorium is dissipated. Desire for food, improved di-

gestion, and with it better color and a better general condition follow. All this is due chiefly to the restoration of the cells of the body to a normal state, and not to the direct influence of quinine upon the cells of the brain, those of the stomach, etc.

Quinine has been viewed from the greatest number of phy siological and therapeutic positions. If we briefly consider all its qualities together, the following may be said: Quinine is a benumbing intoxicant, a febrifuge and an opposer to decomposition. It produces its first results by doses that compared with other alkaloids, for example morphine, are quite large; for this reason the latter are used preferably for narcotic purposes. These narcotic, more powerful alkaloids would, apparently, from the similarity of their fundamental character to that of quinine, act in large doses very powerfully to counteract fever, if their paralyzing influence upon the nerves did not make them dangerous to life. Quinine owes its universal employment, therefore, chiefly to the fact that doses, which to the higher animal are comparatively harmless, have very strong effects on tissue metamorphosis, and the temperature.

Its tonic influence can be effected but indirectly and under certain prescribed conditions. It never exercises a direct effect, because true strength is brought about only by chemical changes. Quinine passes through the system practically unchanged. In well persons it does not act indirectly as a tonic, at least it does not by increasing the appetite or aiding digestion, since both functions are retarded, and nausea is easily produced by it; more strength must be lost by the decreased amount of food than is gained by the smaller accumulations of albumen due to the larger amount of nitrogen, for, according to von Boech, a dog saves by non-poisonous doses of quinine only 5.0 grm. of albumen daily. And as quinine in large quantities diminishes the intensity of the heart's beats and the rapidity of circulation, and also gives rise to a number of other and more unpleasant symptoms, we must regard its effect as weakening, rather than strengthening, on the healthy body. It is quite different, however, in the diseased; for then it is truly a remedy which increases and husbands strength, partly because the desire of the fever patient for food is allayed as soon as the temperature has been reduced by quinine, and because in exhausting diseases (Griesinger, Botkin) it limits the destruction of al-

bumen and of the vital powers, and gives a more tranquil feeling when the body, on account of loss of appetite and the cessation of the process of digestion, refuses to be restored by food. In the last regard, quinine acts very similarly to alcohol.

THERAPEUTIC APPLICATIONS.

Quinine is indisputably one of the most efficacious and reliable remedies in the whole list of drugs. Its qualities have maintained its undiminished popularity, which is excelled by no other remedies but the opiates, in spite of all changes of theories and systems. Its therapeutic uses have, it is true, been limited during recent years in many regards; for quinine is not any more than any other general remedy suited to every kind of complaint, and regarding its efficacy in certain cases, we must be less credulous now-a-days than formerly. On the other hand, the use of quinine in other directions has been greatly extended and better established during the past decade.

There are two indications, above all others, in which quinine is called for without question: 1. To produce its specific effect in malarial poisoning in all its forms. 2. As an excellent antifibrile in many, though not all, feverish conditions.

The beneficial influence of quinine *in malaria-intermittens and malarial intoxication in general* has been determined so many hundreds of times that a mere statement of the fact suffices.

Sydenham first used quinine bark only in quartan and autumnal intermittens. Subsequently he applied it to all forms and at all times of the year. This great investigator formulated a complete method which is known by his name and is still in use.

He refuted the prejudices that prevailed against the then new remedy, which attributed the formation of hepatic and splenic tumors to quinine, as it was also said to cause dropsies—those prejudices against which, however, Stoll, De Haen, and later authors, combated in precisely the same manner, and which, curiously enough, are still met with. Undoubtedly malaria does some times terminate favorably with the use of other remedies, and even when left entirely to itself, but this does not disprove the efficacy of quinine, nor do those rather rare observations of the morbid process

which continue in spite of even judicious application of the remedy, though we do not yet know exactly the causes of its failure in such cases. Sometimes it is likely that the continuance of the intense action of malaria may curtail the effects of quinine, in other cases subsequent observation may show that no intermittent malaria at all was present, and lastly, no causes at all for such failure may be found. As to the various forms and manners in which malaria appears, experience teaches that in pronouncedly pernicious marshy regions quinine has often been used successfully as a preventive, as for instance on the western coast of Africa and in the Southern States of the Union. Statements in this respect are so precise that no doubts can be raised on this score.

The efficacy of quinine is most reliable when malaria, as it generally occurs, appears as a quotidian or tertian intermittent fever with complete apyrexia. The same result is obtained with more difficulty, yet with a fair degree of surety in fevers of a quartian type. Quinine may disappoint in very acute attacks with severe nervous symptoms, with choleriform appearances, etc. (intermittens perniciosa), although even in these, quinine must be considered the only remedy which is powerful enough to thoroughly subdue these pernicious processes. But of all forms of malarial fever, the so-called remittent or paroxysmal with incomplete apyrexia most pertinaciously resists the use of quinine, which is sometimes quite inefficient. The more recent a case of intermittens, the more readily will it be cured by quinine. The relations of arsenic to quinine in the treatment of intermittent fevers have been discussed above.

However, not only the paroxysms of fevers, but also the variegated other appearances and forms of malarial intoxication are controlled by the remedial powers of quinine. We do not take into account the splenic and hepatic tumors which remain as a direct result of the paroxysms and are often cured by this remedy, nor do we count those dropsies which sometimes occur quite acutely without albuminaria after the attacks of intermittens, and of whose real character we are absolutely ignorant. Quinine is not less "specifically" efficient against the large array of symptoms that appear as a disguise of the fever. Some have gone as far as to conclude from the remedial efficacy or non-efficacy of quinine in an inverted manner, that a

malarial process did or did not exist. We need not enumerate all these symptoms: among them are the intermittent neuralgias, the intermittent congestions (ophthalmia, coryza, diarrhœa, pneumonia), and others.

Since the alkaloids of the quina bark have become known, they have been prescribed almost exclusively; they possess, indeed—and, above all, quinine—the most powerful and complete antitypical action, and have legitimately superseded all other remedial means. In sifting the large experiences of former times, we note that the infusion of the bark is least efficient, the decoction acts better, yet more powerfully than the powder, whilst, of course, the alkaloid stands first of all. It is, however, not only preferable on this account, but also for its deranging the gastric organs to a lesser degree, and, as is well known, they are often affected by intermittens (status gastricus) Observation seems, on the other hand, to prove that the proportion of the alkaloid contained in the bark has no direct relation to the febrifuge power of the latter, which means that a larger quantity of the alkaloid is required for the care of an intermittent than is contained in a quantity of bark which is equally effective. Besides, it has been asserted that in the after treatment of intermittents when the paroxysms have been suppressed, but a certain cachexia or so-called "atonic digestive weakness" remains, the preparations of the bark are more suitable than the alkaloid. There is, moreover, no lack of practitioners who, at the present day, upon their own experiences, consider bark superior to quinine for intermittens. Trousseau, for instance, though he conceded that the alkaloid sooner subdues the first attacks, contends that relapses occur oftener after its application, than after the use of bark. Yet generally the great majority of physicians, and we with them, prefer the alkaloids to the other preparations in the treatment of malaria.

The manner of employment of the drug is of great importance; attention has been, therefore, paid to its perfection very early. The first "Roman" method (Torti) consisted essentially in the application of one large dose (8 to 10 grammes) immediately before the attack. But it has been remarked by Sydenham that the drug is often vomited when given in this way, and the object of its administration is then frustrated. For this reason he gave the bark as early as possible before the attack, or immedi-

ately after one. He employed thirty grammes (one ounce) in twelve doses, one every quarter of an hour. As, however, in both modes of application relapses repeatedly occurred, Forti, as well as Sydenham, continued the remedy for some time afterwards.

These methods have been retained up to the present day, and, following Forti, doses are not taken too large, whilst, in accordance with Sydenham, they are not given just before the pyretic attack. The introduction of the alkaloids has added some other amendments. The experiences of good observers (amongst others those of Griesinger) now concur in the following: In simple quotidians or tertians of ordinary moderate severity, it is most expedient to prescribe a larger dose (0.5 to 1.0 grammes of the muriate of quinine), to be given at one, or at most two doses, within from twelve to six hours before the expected attack. When bark be given, it should be administered even earlier. When quinine is given within a shorter period it seldom can suppress the attack completely; it merely weakens or delays it. It is necessary to continue the remedy, though in somewhat smaller doses, on several subsequent fever days, even though the attacks seem to have been subdued altogether by the first dose. If intermittent fever has existed for a longer period, or if there is a continuance of malarial influences, Bretonneau's and Trousseau's method may be employed, viz., to repeat the first dose on the third day, after that again on the fourth, again on tne fifth, on the sixth, and so on during one or two months. Excellent results are also obtained in deeply-rooted quotidian fevers by repeating the original dose daily for several successive days.

In cases where the patient vomits, Sydenham has advised a little laudanum with the drug. As early writers as Stollard de Flaen note that after the last attack no purgative ought to be given, since by evacuations of any description the danger of a relapse is increased.

Of the diversely variegated methods of treatment only a few important points can be noticed here; of others, as for instance the combination with opium, mention will be made in other places. First of all, in intermittens with very short apyrexia, quinine must be given immediately after the attack; in remittent fever generally it should be *given as soon* as the fever decreases. In the same way *with the pernicious* forms large doses (2.0 to 5.0 in

twelve hours) must be given at the slightest decrease of pyrexia, sometimes, in severe cases, during the very attack. Mention should be made of the plan which has been followed very generally in the past, viz.: to let purging or "a general cleaning-out" precede the application of the febrifuge. Whenever marked gastric disturbance occurs, and the Peruvian bark is given in substance, this procedure is not only justifiable but even necessary, because of the digestive troubles which it produces.

Generally, however, the disturbances of digestion are the very result of malarial infection, the equivalent to the pyretic attacks, and the most quickly cured by the febrifuge itself. Since the introduction of the alkaloids gastric symptoms are certainly less formidable and demand less consideration than formerly. In those forms of intermittents in which no perspiration accompanies the conclusion of the paroxysm, bark proves useless, according to the observation of the older writers; it will then be proper to combine it with a diaphoretic infusion (Stoerck, de Flaën).

In the physiological section it has been pointed out in what manner the effects of quinine on the malarial process may be conceived. The most plausible supposition is that it has an immediate effect on the poison of malaria, of whatever kind that may be. Other hypotheses are, in the present state of our knowledge, not worth mentioning here.

As quinine was of such pronounced efficacy in typical malarial fever, it was easily supposed that it might be useful in intermittent feverish attacks of other diseases which sometimes resemble the regular quotidian or tertian type. Such pyretic attacks may occur with deep-seated suppuration (hepatic abcesses or purulent puerperal gatherings), in phthisical processes, with pleuritic exudations and so forth. Experience teaches us that quinine will *sometimes* suppress the attacks or weaken their severity. The fundamental pathogenetic action, however, is, of course, seldom touched by it, even in case of a favorable effect on the fever. But the latter is also an unreliable one, as often even large doses make not the slightest alteration in the violence and appearance of the attacks. It is impossible to account for such different effects. One might judge that quinine would be the more powerful the more pronounced the regular type of the fever is. But such a supposition is erroneous. We may see hepatic abcesses with the most *deceptive quotidian* fever which are not modified in the

least by quinine. And we particularly note that in the intermittent fever of phthisical patients, even after large doses, very rarely an effect can be produced. Though it is generally stated that quinine is efficient in such cases, numerous observations of consumptives with intermittent and remittent fever brought us to the conclusion that the antitypical effect of the drug is scarcely more unreliable in any other condition. The experiences made in the Franco-Prussian war have taught, however, that early application of very large doses in the septicemic processes in the wounded often yielded surprisingly favorable results, though this happened in combination with the use of considerable quantities of wine. This, of course, obscures the question of the efficacy of quinine in septicemia.

Quinine, above all other similar remedies, is peculiarly efficacious in abating high temperature in continuous fevers, and in this action only salicylic acid at all approaches it. But as the theoretical discussion of this antifebrile action has been sufficiently treated under physiological considerations, we may confine ourselves here to mere practical points.

The general opinion is that quinine can be dispensed with in genuine inflammatory processes, as in the inflammation of the serous membranes, in phlegmons, articular inflammations, etc. The fever of these cases is but rarely dangerous in itself; it decreases with the decrease of the inflammatory process to which its rise and fall bears direct relations, whilst the treatment has to be directed towards the former. When we employ quinine in the higher degrees of the fever, we find the decrease caused by its use rather small, evanescent and of little effect on the course of the disease. All diseases in which this remedy has been applied, with more or less good results, as an anti-febrile, are reckoned to-day amongst the infections, or, maybe, constitutional diseases—obviously, we cannot enter into a discussion upon the propriety of such an idea.

Typhoid Fever (typhus abdominalis) has been pre-eminently combated with distinctly favorable results by quinine. The drug is generally given as an adjunct to the cold-water treatment and combined with it. We do not feel called upon to compare the relative values, but should we be compelled to select either of them, we agree entirely *with* Liebermeister's opinion, and, all other things being *equal, prefer the* quinine treatment to the hydropathic one.

Generally a dexterously administered dose of quinine reduces the temperature and abates all the symptoms connected with it, the high pulse and the dimness of percepception, at the same time the dangerous consequences of a continuous high temperature, especially its bad influence on the cardiac muscle, are prevented. Our aim must be to bring down the temperature as near possible to the normal, and the dose must be measured accordingly. It must be large in severe fever, and ordinary during the first two weeks' course of the disease. Reduction will be observed in some hours; it will be greatest after 8 to 12 hours, and will, in severe cases, still be marked after 24, and even 36 hours. (Compare our statements about salicylic acid.)

The mode of administration is important. Experience has sufficiently demonstrated that for obtaining an antipyretic action large doses (not such as are adapted to children, 0.2 to 0.3 grammes, but doses of 1.0 to 3.0 for adults) are necessary; some physicians push them in severe and pertinacious cases even to 5.0 grannes.

It must be considered an absolutely necessary condition to introduce this dose of 1.0 to 3.0 at a time or at least within one half or one hour; when it is distributed through a whole day it becomes useless. The result aimed at, viz., the reductionof temperature to its normal degree, will be best obtained, if the remedy is given in such a manner that the acme of its effect coincides with the natural fall of the daily curve, or, according to the principals we have just enunciated, in the evening between 6 and 9 p.m. There appears to be no important difference between the action of the sulphate or muriate, nor have we noticed any between the action of a solution and that of powder, but it is more easy with the latter when given in bolus or capsules, to spare the patient its bitter taste. Repeating the dose must be decided upon according to the state of the fever. No repetition should be made within twenty-four hours and when no very dangerous rise has taken place, the application of the dose on two successive evenings ought to be discontinued on the third; however, if necessary, it will have to be continued for four or six evenings. It requires no further elucidation to show that this treatment, combined with the cold bath, will aid the attainment of the desired results. Neither is it necessary to point out that in very severe cases of malarial intoxication, quinine may be as powerless as the hydro-

pathic treatment. But only a superficial observer can therefore disparage it altogether; such disparagement may be permitted some day when a specific antidote has been found for the poison of typhoid fever.

The success of the quinine treatment in abdominal typhus is much less than in other infectious diseases, which, according to the present nomenclature are designated as "typhus." In recurrent fever it is wholly or almost wholly useless, as for *typhus exanthematicus*, the observations do not as yet seem conclusive. In regard to *acute febrile eruptions*, reports differ widely. Should the use of quinine in them actually appear indicated, the methods of application would be the same as in typhoid. In croupous pneumonia quinine has supplanted the other antiphlogistic measures hitherto employed (digitalis, veratrum and others), and quite properly so, according to our mode of thinking. When direct treatment of the fever is indicated in this disease, and cold baths cannot be administered for any reason, then quinine in large doses is decidedly the best means to reduce the temperature. Juergensen has given as much as 5.0 grammes in pneumonia. In acute articular rheumatism the quinine treatment has been at present entirely replaced, at least, in Germany, by salicylie acid. This treatment has nowhere achieved any importance except in France (Bisquet), because of its unreliable action, and is mentioned, therefore, only because of its historical interest.

That bark, which has been used traditionally in preference to the alkaloid, in combination with mineral acids should have any effect or act specifically in scorbutic affections (morbus maculosus, Werlhofü) and similar diseases, is wholly unproven.

Preparations of quinine are in very common use as remedies to aid digestion and as tonics. They are given in a slip-shod manner in expectancy of particularly good results, in cases of failing appetite and in the most diverse cachectic and other conditions of the system caused by inanition, in simple dyspepsia, in symptomatic dyspepsia ("atonic weakness of digestion") of phthisis, to patients who are weakened by long suppuration or loss of blood, to convalescents from typhus or from pleurisy, and so forth. How unstable the foundations of such a treatment are, we have pointed out before. Continued observations have thoroughly convinced us of the utter futility of the indication for quinine on merely practical grounds: quinine is by no

means a directly "strengthening" remedy; a good piece of beef, wine, milk, eggs, but not quinine, strengthen the convalescent from typhus and the feverless sufferer from pleurisy. Nor is quinine of any value as an appetizer in certain forms of dyspepsia, less even than the mere aromatic bitters. In our opinion its use in this direction ought to be limited. In these cases it should be given in doses of 0.02 to 0.05.

The alkaloids of quina have been used in the different neuroses of sensibility and mobility. We have stated that these affections (neuralgia, convulsions) disappear under the use of quinine, when they are caused by malarial poisoning and when they show a typical rythm; but experience demonstrates that such ailments will sometimes yield to quinine when they are not based on malaria. No certain rules can be laid down for its application; our collected materials only enable us to say that quinine was generally prescribed in such cases without definite plans because all other remedies had failed. Most frequently it proved successful in cases of neuralgia, for which no cause could be found. Scarcely any result can be expected from it in the neuroses of mobility (epilepsy, chorea). But sometimes surprising successes have been obtained in conditions where we are wholly at a loss to find the reasons for it. Cases have been reported in which extremely severe singultus was cured by one large dose of quinine; we have seen high-graded *delirium cordis* with palpitations (probably caused by chronic nicotine poisoning), after it had lasted atypically for months, disappear for a number of days completely by means of two large doses of quinine (1.0 gramme each).

Quinine has been recently recommended by several observers for *tussis convulsiva* (Binz, Breidenbach, Heffen, and others) as having been surprisingly successful in uncomplicated cases. Sufficiently large doses must be taken, according to the age and the severity of the complaint (from 0.1 to 1.0 per day.) In whooping cough it is used not only internally but also by brushing the pharynx and glottis (Hagenbach), by insufflation into the larynx and trachea (Letzerich), and by inhalations. Helmholtz succeeded in arresting hay fever in himself by injection of a quinine solution into the *choanæ*. Further observations have proved that such attacks were at least moderate; others, however, failed to do even that.

For a long time quinine has been in use for all kinds of

splenic tumors, and recently so for those caused by leucæmia; it appears that sometimes—though rarely—a steady continuance of large doses may arrest the leucæmic process, if this treatment is commenced sufficiently early (Mosler, Hewson, and others).

In our times, quinine is very often employed hypodermically but almost exclusively in the treatment of intermittent fever. That this treatment can be perfectly successful is beyond doubt; but its inconvenience is the injection of too large a quantity of the solution, and it has therefore become limited to those cases in which the drug is refused by the stomach and vomited, or when severe derangements of digestion and the nature of the fever (febris perniciosa) require rapid action.

The old endermic method of application has become completely superflous by its hypodermic use. The application of quinine in an ointment on the intact skin (for the sake of a "general effect") merits mention only because of historic interest. It is also often applied in an enema as an antipyretic in fevers when the patient suffers with uncontrollable vomiting.

For external use bark is more important. It is applied to atonic foul ulcers in cases of gangrene; also as an ingredient of tooth-powders for bleeding gums. However, we possess remedies that act better in these cases, and are cheaper than quina. Bark can be, therefore, dispensed with as an external agent.

THE ALKALOIDS OF QUINA AND THEIR PREPARATIONS.

1. Quininum is not used therapeutically. Starke and Muennich give the following directions to make the basic alkaloid more palatable: quinine combined with small quantities of tartaric acid is readily dissolved by its hygroscopic water after a while, or still more quickly by the addition of a few drops of water, and the most concentrated solutions of quinine salt may be prepared in this way for subcutaneous injection. If to the doughy mixture of quinine and tartaric acid sugar is added, several grammes of the alkaloid may yet be comprised in the bulk of a pill not larger than the size of a small cherry, which can be easily be gulped down with a mouthful of water, without the tongue becoming affected by the taste of quinine.

2. Quininum sulphuricum, basic sulphate of quinine. Small, slender, colorless, prismatic crystals of intensely bitter taste, which are soluble in about 80 parts of cold and 30 parts of boiling water, in 60 parts of alcohol, and very readily in ether. To increase the solubility in water *a few minims* of sulphuric acid are generally added. Given as a *stomachic in doses of* 0.02 to 0.05; as a febrifuge of 1.0 5.0 to (see above),

powders, capsules, pills, and in solution. For hypodermic purposes a quarter or one half of these doses are used.

3. Chininum hydrochloricum seu muriatium, muriate of quinine; crystalizes in white, silk-like, shining needles, which dissolve quite readily in water. It is given in the same way as the sulphate, and because of its greater solubility is much better adapted for internal use, especially with an addition of a little muriatic acid; the form of application and amount of dose being the same as for the sulphate.

Besides the above mentioned, a number of other quinine salts have been proposed for therapeutic use; but none of them appear preferable, and none has obtained any extensive use. The doses and applications are the same as for the other salts. The following are officinal:

4. Chininum bisulphuricum is comparatively easily soluble in water (8 to 10 parts), and spirit (2 parts).

5. Quininum ferro-citricum.

6. Quininum tanicum.

7. Quininum valerianicum.

8. Cinchoninum (of much weaker action than quininum).

9. Cinchoninum sulphuricum, sulphate of cinchonine; colorless, prismatic crystals, soluble in about 60 parts water, and in about 7 parts of alcohol; insoluble in ether; very bitter. Its solubility in water is increased like that of the corresponding quinine salt by the addition of a few drops of sulphuric acid. The mode of application is like that of the quinine salts, but the doses are by one half larger. It is useful in the lighter cases of intermittents, but not applicable to the more severe ones, as its action is less certain and slower than that of quinine.

10. Chinioideum, chinioidinum; a resin-like, dry substance of brown color; little soluble in water, easily in alcohol. This very cheap preparation is, on the whole, a mixture of quinine, cinchonine, quina, red and resinous matter. Its action, on account of its variable composition, is very uncertain. The doses are considerably higher (two or three times) than those of the alkaloids; either in pills or in alcoholic solution.

11. Tinctura Chinioidini; 2 parts quinine, 15 parts spiritus vin. rectificat., 1 part hydrochloric acid; of red-brown color; ½ to 1 teaspoonful in aromatic liquids. The application is subject to the remarks made on chinioidine.

12. Conchinine, a recently introduced quina-alkaloid (O. Hesse) which crystallizes in slender, long, silk-like, shining needles; bulky, and with difficulty soluble in water; of very bitter taste. According to Wunderlich, v. Boeck, Ziemssen, Macchiavelli, and Strümpell, it acts on putrefaction, fermentation, in intermittent and typhoid fevers, erysipelas and puerperal conditions, similar to quinine, but without causing the same unpleasantness to the patient (tinnitus aurium). Dose: 1.0 to 3.0 grammes in powder in the evening.

Bark and its preparations:

1. Cortex Chinæ calisayæ.

2. Cortex Chinæ fuscus.

3. Cortex Chinæ ruber.

As an antitypic quinia barks are no more in use, and require larger doses than the other preparations. Smaller doses (0.3–0.5) in pills, powders, or best in infusion or decoction (the latter preferable, as containining more of the active principle). Externally as powder or decoction (15.0 to 30.0, add 200.0).

5. Extractum Chinæ fuscæ, a powder which forms a turbid solution in water; internally 0.5 to 1.5, in pills or solution, several times a day.

6. Extractum Chinæ frigide paratum contains very small quantities of alkaloids, and is therefore totally useless.

7. *Tinctura Chinæ*, prepared from cortex chinæ fuscus; color, reddish-brown; 20 to 50 minims.

8. *Tinctura Chinæ Composita, Elixir Robarans Whyttii*, 6 parts cort. chinæ fusci pulv.; 2 parts rad. gentianæ; 2 parts cort. fruct. aurantii, macerated with 1 part of cort. cinnamoni, and 50 parts of dilute spirit. Color, reddish-brown; dose: 20 to 50 drops.

9. *Vinum Chinæ*, 5 parts cortex regius, with 100 parts of red wine, tea or tablespoonfuls. A favorite preparation, but nevertheless not a useful one. We prefer not to embitter the taste of the wine and to prescribe each separately where both bark and wine are indicated.

The following are said to act like quinine and the other alkaloids of bark:

Bebeerine, the alkaloid of the bebeera bark (nectandra rodiai), and perhaps that of buxus sempervirens, acts least upon processes of putrefaction, and on the lower organisms (Binz). No minute researches are known to have been made regarding the higher animals. Dogs are said to exhibit after doses of 1.0 gramme gastric (vomiting and purging), and general symptoms of poisoning (weakness, giddiness). Therapeutically the drug seems useless, and is not prescribed by us.

Piperine.—Compare the peppers.

Many non-alkaloid bitter substances have been suggested as cheap substitutes for quinine, such as salycine, gentian, quassia, etc. They have been tried, but have not yielded, even remotely, similar results.

THE ALKALOIDS OF THE COFFEE TREE, OF CHINESE AND PARAGUAY TEA, OF GUARANA, COCOA BEANS, AND OF THE COCA LEAVES.

The identically same alkaloid which is found in the leaves and beans of the coffee tree, originally a native of Western Asia and Eastern Africa, is the Paraguay tea, the favorite beverage of South America, in the paullinia shrub, the black seeds of which are used in Brazil for the preparation of a refreshing lemonade, and lastly in the cola nuts which grow on the Guinea coast, and furnish the coffee of Soudan, is now generally designated as caffeine or coffeine, but was, before its identity was recognized, named after the plants it came from, as caffeine, theïne or guaranine.

In the seeds of the cocoa tree theobromine is found, and *in the leaves of the* coca shrub the cocaine and hygrine.

All the above-mentioned plants have in common that they

were received in the course of time amongst the most favorite articles of man's consumption, because of the peculiar reviving and exciting action which their alkaloids exercise on the nervous system, and the slightness of the intoxication which they bring about, so that their regular moderate use throughout life proves harmless, while other stimulants generally do not.

The effects of these plants on the human organism depend, however,' not only on the quantities of alkaloid which they contain, but also on other ingredients. Even the coffeine plants differ in many respects as to their action; still much more so do the theobromine and the coca plants. We will the reforeconsider first the action of the pure alkaloids; then that of the plants of dietetic consumption.

CAFFEINE.

The faintly basic alkaloid, prepared from the before-mentioned plants, caffeine, $C_8H_{10}N_4O_2$, or $C_5H(CH_3)_3N_4O_2$, can be considered to be a methylated derivate of xanthine, and according to its composition, may be called trimethylxanthine, or methyl theobromine. It crystallizes with one molecule of water in very thin, long, colorless, shining prisms, of a faintly bitter taste, is not easily soluble in cold water and alcohol, is easily soluble in hot water; with the strong mineral acids it forms salts that are easily decomposed, and by boiling with baryta water it is transformed into a strong base called caffeïdine, $C_7H_{12}N_4O$; the latter when boiled for a longer period with a superabundance of baryta will split up into ammonia, methylamine, methylglycocol, and formic acid.

PHYSIOLOGICAL ACTION.

The brain is affected by caffeïne in a similar manner as by morphine, but with this difference, that the caffeïne excitement lasts longer; the caffeïne stupor passes off more quickly than the corresponding effects of morphine, as do all of the caffeïne symptoms. There is also a similarity in the action on the spinal cord, whilst, however, morphine causes only in frogs, a reflex irritability of high degree and tetanus; but in the mammals it produces mere increased reflex irritability (never tetanus), which soon afterwards decreases; caffeïne possesses tetanic action in all hitherto tried mammals. To take the spinal medullary action of caffeïne is not equal to that of strychnine, as in cold-blooded animals and mammals a hundred times, and in man two hundred times larger quantities of caffeïne are required in order to produce tetanic effects, as will be made clear by comparing the below-mentioned tetanic doses of caffeïne with those of strychnine. Regarding men we can positively discern only an increase of reflex irritability, as tetanic effects failed to appear even after a dose of 1.25 grammes. Since strychnine acts neither on the brain nor on the heart and on the arterial pressure in a directly contrary manner, caffeïne, viewed from a physiological standpoint, must rank

nearer morphine. The action of caffeine on the muscles of the rana temporaria cannot be identified with the muscular effects of veratrine, and for the present has no analogue.

Absorption and Excretion.—Caffeine is absorbed into the blood by all the mucous membranes and by the subcutaneous connective tissues. It is then found in different organs, and is again excreted undecomposed in the urine and bile (Strauch).

General Effects.—In frogs the general effects differ according to the species. In the rana esculenta the reflex irritability is greatly increased by 0.002 grammes of caffeine, so that reflex clonic spasm sets in, as after the use of strychnine. In the rana temporaria, on the contrary, not a trace of increase of reflex irritability or of rigor appears at first, but a peculiar stiffness of the muscles shows itself very quickly at the site of introduction and extends very slowly to the more distant organs.

While, therefore, the muscles first affected appear quite stiff and contracted, wholly insusceptible and dead, the more remote muscles may still be quite normal and easily excitable.

On the second or third day of poisoning, as these differences partially disappear, the rana temporaria may experience increased reflex irritability and, occasionally, weak tetanic convulsions, while, on the other hand, the R. esculenta shows an unmistakeable stiffening of the muscles which, however, is never so violent as in the other species (Schmiedeberg). In like manner all warm-blooded animals which have hitherto been investigated (rabbits after 0.12 grm., cats and dogs after 0.2 grm. of caffeine, have been injected into a vein), shrink back as if poisoned with strychnine, or fall into a state of rigor whenever shaken or touched, and frequently without any demonstrable external impulse (Albers, Falck and Stuhlmann, Voit, Aubert, and others). Frogs, like warm-blooded animals, are finally paralyzed (after this irritability and rigor have passed off) when very large doses are given, and die of general paralysis. Upon men doses smaller than 0.3 grm. have no demonstrable effect; 0.36 grm. produces merely a swimming in the head, which passes away in an hour. When 0.5 grm. is taken the frequency of the pulse is increased a trifle (about 4 beats), but this effect is transient. After an hour a transitory cerebral numbness sets in and the hands commence to tremble,

but only for a very short time. In one case in which a total quantity of 1.22 grm. was taken in six days, on the tenth day from the commencement of the experiment a few quite painful hemorrhoids appeared. The patient had never been troubled with these before. They disappeared without treatment in the course of the next eight days. As in dogs poisoned with caffeine the veins, especially those of the mesentery, have always been found greatly distended; it is not improbable that the hemorrhoids mentioned resulted from the uses of caffeine (Aubert). The smallness of the effect caused by the above doses in Aubert's case may be due to the circumstance that he was probably more habituated to caffeine by reason of long use of coffee.

Other experimenters (C. G. and J. Lehmann) perceived much more marked symptoms of poisoning after the same doses (0.3–0.6 grm.) These symptoms were violent excitement of the vascular and nervous systems, increased frequency of the pulse, irregular and often intermittent pulse, oppression of the chest, headache, ringing in the ears, appearance of stars before the eyes, visions and mental aberration, delirium, insomnia, erections, urinary tenesmus. Caron's symptoms after the same dose (0.5 grm.) were headache, trembling, nausea, protracted drowsiness and reduction of the pulse by 30 beats per minute. Kelp observed in the case of a very delicate and nervous woman, who had taken 0.48 grms. in all, the following still more severe symptoms: vertigo, faintness, violent precordial anxiety, very rapid pulse, abdominal pulsation, violent trembling of the extremities, audible chattering of the teeth, swimming of the head, and convulsive sensations in the neck and throat. This state lasted three hours, and did not entirely disappear until after the expiration of twenty-four hours. Some care should therefore be taken in giving caffeine, less on account of any danger of death, than because of these frightful and terrifying symptoms. The greatest dose yet taken (1.5 grms.) is that employed by Frerichs upon himself. After a quarter of an hour his pulse became full, hard, and quicker (by ten beats), his head heavy and swimming, and vertigo and ringing in the ears were experienced. His disquiet and excitement were such that it was impossible to keep a fixed idea. On the expiration of an hour vomiting set in, after which the symptoms gradually disappeared without any after-effect.

Men and all classes of animals can become accustomed to

continually increasing doses. Severe symptoms of caffeine poisoning, when they occur, always disappear very quickly.

EFFECTS ON INDIVIDUAL ORGANS AND FUNCTIONS.

Central Nervous System.—The activity of the brain is first increased and then diminished, as is clearly shown by the above-cited reports, in which exhilaration is followed by stupor in men. The observation that different individuals experience greater or less excitement and stupor, that one is rendered sleepless, another sleepy, according to habit and constitution, may be made of all drugs which act in a similar manner, such as morphine, alcohol and chloroform. The same is true of the facts that in men, the effect on the brain preponderates over that on the spinal cord, and that in the latter tetanus takes place as the result of excessive reflex irritability, while in the former reflex irritability is merely increased. On account of the similarity which the action of caffeine on the brain and spinal cord bears to that of morphine and, to some extent, that of strychnine, it is unnecessary to trace the symptoms of the former separately. We refer, therefore, to what has been said concerning the action of morphine on the brain, and that of strychnine on the spinal cord.

According to the detailed statements made above, the spinal cord of the Rana temporaria is not affected by caffeine, while that of the R. esculenta experiences an unquestionable increase of reflex activity. It would be wrong to infer from this that the cords of these species are differently constituted, or possess different degrees of sensibility to caffeine, since the behavior of the two species under the influence of strychnine is identical. It is therefore much more probable that the cord of the R. temporaria is not affected by caffeine, simply because this alkaloid is very evergetically retained by the muscles of this species, and is thus prevented from rapid diffusion and reaches the cord in very small quantities or not at all. In fact, those muscles, likewise, that are remote from the place of introduction, remain long free from the influence of the alkaloid and in a normal condition, while the nearer muscles are at once stiffened and killed. (Schmiedeberg.)

The Peripheral Nerves and Striped Muscles.—When given in the usual manner internally, caffeine attacks the brain

and spinal cord long before it affects the peripheral nerves.

No effect upon either sensory or motor nerves has yet been proved. (Bennett alone mentions paralysis of the sensory nerves.) A motor nerve, however, placed in solution of caffeine, or a sensory nerve near a place of hypodermic injection, soon becomes paralyzed. (Eulenburg.)

Of the greatest interest is the change in the striped muscle of Rana temporaria, first observed by Voit and more closely studied by Johannsen. This commences in the muscles adjacent to the place of injection and advances very slowly to more distant parts. The muscles are white, bloodless, stiff and contracted, aud present the exact appearances of the rigor produced by heat. If a muscular fibre is observed under the microscope during the introduction of caffeine, the contents of the cell are seen to move, the transverse striation disappears, the longitudinal stripes become very plain, the fibre shortens by nearly half its length and the sarcolemma peels off in places. The same appearances are presented by poisoned muscles in the living body. The curve drawn by a muscle so poisoned, and not yet quite stiff shows a very marked prolongation of the falling curve. (Buchheim and Eisenmenger.) When the muscle is completely stiffened it of course does not contract. Rinsing the fibres in a 0.6 per cent solution of common salt does not prevent the stiffening. It is indifferent whether the muscles are cut loose from the nervous centre or retain their connection with it through the nerves.

The muscles of curarized animals also fall into this condition. The conclusion must therefore be drawn that this action of caffeine is a direct action on the muscles. In Rana esculenta, as already mentioned, there is no such effect, or only a slight one after the alkaloid has acted for days.

The only statement concerning any such effect in warm-blooded animals is the doubtful one made by Johannsen that cats exhibit a similar stiffening of the muscles but in a lesser degree. Other observers have said nothing upon this point. We (Rossbach and Harteneck), have experimented upon living rabbits: doses of 0.05 grm. of caffeine injected into the jugular vein produced a marked acceleration of fatigue, so that the maximum of the contraction curve fell in one experiment from nine to two mm. in 600 contractions, *though the muscle was living*, traversed by blood and little

fatigued. Johannsen's theory of the muscular effect of caffeine fails, therefore, in the case of rabbits; at least, for such small doses.

This theory says: "Large doses produce distinct rigor mortis, small doses probably produce only the invisible first stage in which the jelly-like myosin is excreted. If the chemical process of this first stage of rigor mortis is identical with that of muscular action, as Herrmann thinks, the assumption that small doses of caffeine facilitate muscular action, gains great probability."

Respiration, as long as the reflexes are increased, is first accelerated, afterwards retarded. This is plainly due to processes in the respiratory centre, similar to those going on in the rest of the spinal cord. Tetanus due to caffeine can be removed by artificial respiration, according to Uspensky and Aubert.

Circulation.—The heart-beats of a frog poisoned with large doses of caffeine are of reduced strength and frequency.

When the heart is removed from the body and placed in caffeine dissolved in solution of common salt, a great increase in the pulsations first takes place, followed after a minute by a rapidly increasing retardation, and in a short time the heart becomes white and stiff in systole. The change is therefore like that in the striped muscles of the trunk.

The hearts of warm-blooded animals beat more rapidly at first after small or moderate doses of caffeine.

The pressure of the blood rises (Levin). Only after comparatively large doses have been injected immediately into the jugular vein does a fall of pressure appear, together with acceleration of the pulse (Aubert).

After very large doses the frequency of the pulse is diminished again, falls below the normal, arhythmia sets in, the pressure continues to fall, till at last the heart stops in diastole, greatly distended with blood.

Aubert considers the initial increase of frequency as due to stimulation of the accelerating apparatus of the heart, rather than to paralysis of the vagus nerve. To explain the simultaneous occurrence of the smaller pulse-waves and the fall of blood-pressure observed in his experiments upon animals, he assumes a peculiar kind of heart-fibres, *the cardiotonic*, which become weakened, and finally paralyzed. This causes the heart to act with little effect,

though despite the increase in frequency. We know nothing as yet of the effect on the vasomotors; but as Voit has observed a vascular paralysis in the frog, a similar action may be the cause of the reduction of blood-pressure in warm-blooded animals.

We have noticed, under general phenomena, that increase of pulse-frequency always occurs in men.

The Temperature is not changed by small doses of caffeine; but moderate doses, too small to cause symptoms of convulsion, produce a rise of 0.6° C. Doses large enough to produce distinct muscular rigidity, disquiet and salivation, raise the temperature 1.0° to 1.5° C. in one or two hours (Binz).

We know very little concerning the action on the digestive apparatus. The secretion of the sweat and salivary glands is promoted according to Hannon and Peretti. Vomiting is often observed after large doses. Peristaltic motions are not increased or altered (Nasse). The abdominal veins are greatly distended with hlood; the reason therefor is not known.

The Secretion of Urine appears to be increased by caffeine, but this is not thoroughly established.

Concerning tissue metamorphosis after the use of caffeine, the experiments of Hoppe, Rabuteau and Roux show in some cases an insignificant decrease, in others an increase in the elimination of nitrogen. Their experiments, however, as Voit remarks, are not free from error. The only unobjectionable experiments are those of Voit himself, which, however, were made with coffee, not with caffeine, and it would be erroneous to consider the effects of the two upon tissue metamorphosis as the same. For this reason we do not give Voit's results with coffee, and can only say that the effect of caffeine upon tissue metamorphosis is probably insignificant, or, at most, produces a slight acceleration.

Roux states that the initial increase of urine and of the excretion of the chlorates disappears when the patient becomes habituated to caffeine.

Therapeutic Applications. The medicinal use of caffeine is very limited.

Its greatest reputatation has been gained in hemicrania, which it sometimes cures, according to various observers; but it more frequently causes merely a shortening and reduction of the separate paroxysms, and often has no

effect whatever. The reason of these differences is probably the variety in the form of the disease. We have given it in so-called *Hemicrania sympathico-tonica* without effect, but better results may probably be looked for in unilateral headache of the hysteric and anæmic kind, or in other still obscure forms of the disease.

The effect is better (Eulenburg) when it is given in rather large quantities at the beginning of the attack, than when given in small doses between the paroxysms. In general headache, also, which seems to be located in the interior of the head (without hyperalgesia of the skin), a frequent symptom in chlorotic and hysteric persons, the use of caffeine is often beneficial.

Caffeine has been employed in various other affections, to promote diuresis in dropsy proceeding from heart disease, as an hypnotic, etc., but it has not proven reliable.

Doses.—Caffeinum is given either pure or in the form of a salt, of which (not official) compounds caffeinum citricum and caffeinum lacticum are most used. These are usually given in small doses of from 0.05 to 0.1, but French physicians begin with much larger doses (0.5), and increase the dose to 2.0 or 4.0. Pastilles are the most convenient form on account of the bitter taste, but powders, pills, or a solution of the salt may be employed.

ALIMENTS CONTAINING CAFFEINE.

1. *Coffee.*

The proportion of caffeine in the raw coffee bean (from coffea arabica) varies, according to a comparison of the results of Brill and Aubert, from 0.2 to 0.8 per cent, according to variety, season, etc.

Very little caffeine is lost in roasting, even when the beans are greatly burned. Most of the caffeine in the roasted and ground berries passes into the beverage, scarcely a fifth part remaining behind (Aubert).

The coffee prepared from a quantity of berries weighing 10 0 grams in the raw state will therefore contain, on the average, from 0.1 to 0.12 grammes of caffeine (Aubert). In addition to caffeine (0.2 to 0.8 per cent) the raw berries contain the following ingredients.

Legumine	15 per cent.
Sugar and gum	55 "
Fixed and volatile oils	13 "
Ash (potassium, sodium, magnesium, oxide of iron, phosphoric acid, chlorine)	7 "
Caffeine, tannic and caffeic acids	5 "

In roasting, decomposition of the legumin and sugar produces volatile empyreumatic ethereal oils and caramel, the former of which give coffee its agreeable odor and taste. The berries lose from $\frac{1}{8}$ to $\frac{1}{4}$ of their weight according to the extent of roasting (Aubert).

Physiological Action.—In addition to caffeine the other ingredients,

especially the aromatic oils, the salts and the hot water have an important part in the action of coffee as a beverage.

Indeed Aubert and Haase are led by their experiments to doubt whether *caffeine is the most active principle in the infusion of coffee.*

They give the following reasons: Coffee exerts a much greater poisonous effect upon men than pure caffeine in quantities equal to those contained in the beverage. Coffee containing 0.4 grammes of caffeine has as powerful an effect as 1.5 grammes of pure caffeine. Rabbits into whose jugular veins coffee containing 0.04 grammes of coffeine has been injected die very soon, with trembling, great disquiet and convulsions; whereas 0.05 gramme injected in the same manner not only fails to cause death, but produces scarcely any abnormal changes.

While caffeine entering the system through the blood produce no change in the persistaltic motion in rabbits, coffee introduced in the same way causes a brief tetanic contraction of the bowels. If the residue of the infusion, entirely free from caffeine, is injected into the veins of rabbits it immediately produces death with convulsions, almost instantaneous stoppage of the heart, dyspnœa, but no tetanus.

Frogs also are effected by this residue to a much greater degree than by caffeine, and in a totally different manner (no tetanus being produced). Hence it appears that this residue containing no caffeine is certainly active, and that its action is quite different from that of coffee. But Aubert could not determine to what substance this effect is due, as coffee contains 1.5 per cent of potassium (calculated to the roasted berries). Aubert, with the then prevalent exaggeration of the poisonous character of potassium, thought that the effect might be ascribed to this ingredient. We, however, have shown that the quantities of potassium taken in coffee can have no possible effect on human or animal organisms, at least when taken through the stomach. Nor can the small quantity of tannin have any effect worth speaking of. It remains to consider the empyreumatic substances formed during roasting (the caffeon of Boutron) the chemical character of which, however, has not yet been investigated.

According to Lehmann, Nasse, Marvaud and Binz, these produce, when given alone, a pleasant exhilaration of the intellect rather than the fancy; acceleration of the heart's action, but reduction of blood pressure; accelerated and more violent respiration; absence of the feeling of hunger, accelerated motion of the bowels, increase of water in the urine with decrease of the solid constituents and urea.

Caffeon differs from caffeine, therefore, principally in having an effect on the motions of the intestines and in lowering the temperature. Although nearly overy one in the civilized world drinks coffee, our knowledge of its action is very defective, since those who are willing to experiment upon it in a scientific manner have already become so accustomed to its use that very large quantities are required to produce clearly recognizable changes in the bodily or mental condition.

The following description, therefore, after Boecker, Moleschott and Aubert may be taken as correct in general, but liable to many individual exceptions. Coffee prepared from the usual quantity, 15.0 grammes of berries, and drunk hot, has a bitter taste. It is followed by acceleration of the pulse, and general feeling of warmth (due to the hot water). The secretion of urine is increased. The power of thought is stimulated, and *the imagination* becomes livelier. The sensibility to impressions *on the senses is* increased, the judgment made more decisive. As the

fancy is also stimulated, however, the thoughts and mental images rapidly change so that coffee is more favorable to the moulding of ideas that have been already thought out, than to the rough casting of newly arisen thoughts(?)

Coffee counteracts the stupifying effect of alcohol, wherefore, it is much sought after excessive carousals.

Aubert, after drinking strong coffee (made from 50.0 grams of roasted berries), found his pulse increase gradually from 64 to 72 beats per minute. Headache, vertigo, trembling and numbness in the hands and feet, nausea, and a feeling of heat running periodically over the body, ensued. Many fall into a state of excitement resembling intoxication, and become sleepless, while others are stupified and made drowsy by very large doses. For the rest, the symptoms produced even by the largest quantities of coffee disappear with surprising rapidity. A woman who drank at once the coffee made from 250 grms. of berries, was affected with frightful anxiety, shortness of breath, muscular contractions resembling chorea, unusual bodily and mental disquiet, together with great dulness of the sensorium. Respiration was fatiguing, short and frequent (30 to the minute), the beating of the heart remarkably strong, the arteries much contracted, the pulse hard and filiform. An hour after the coffee had been taken there was an inclination to vomit, and violent diarrhœa with little pain but strong tenesums. Micturition was very frequent, every fifteen minutes.

All symptoms of poisoning disappeared in forty-eight hours (Curschmann).

Moderate quantities of coffee may be taken throughout a long life without any result; the use of coffee gradually becomes a necessity, as in the case of tobacco and alcohol, and its deprivation then causes unpleasant consequences, especially melancholy and incapacity for mental work. Very protracted use of exceedingly strong coffee, on the contrary, at last affects the appetite and digestion, and leads to a high degree of abnormal nervous irritability.

Nutritive value.—It has been claimed for coffee as for alcohol, that it is not only a beverage, but an article of food. It has also been observed that many, by using much coffee, have been enabled to dispense with other food to a great extent, and that its use diminishes the excretion of urea. It has hence been thought that coffee is able to check tissue metamorphosis in the body, and that it is therefore an economizer. These and other still more improbable theories were not confirmed by Voit's exact experiments on dogs, in which an increased rather than diminished elimination of nitrogen was found.

The importance of coffee is therefore due to its beneficial and pleasing stimulation of the nervous system. By this the tissue metamorphosis is slightly increased, and the absorbed food is used rather more quickly than usual; no economy, therefore, takes place. The stimulation produced by coffee in dietetic doses, does not pass into depression as with alcohol and other stimulants, but imperceptibly gives place to the normal, nervous, and psychical condition. Hence it is far preferable to other stimulants. It is still very doubtful if the small quantities of albumen contained in the berries, pass into the hot infusion. Direct analysis gives no evidence of albumen in the beverage. At all events the quantity is so small that coffee can have no appreciable nutritive value.

Dietetic and Therapeutic Employment of Coffee.—As the medicinal use of coffee is of far less importance than its employment as an article of

diet, we will first describe the latter. Coffee is used as a daily beverage by millions, without being followed by any abnormal symptoms that can be referred with certainty to its use. This fact alone is in striking contradiction to the unconditional condemnation of coffee-drinking. Doubtless it is no more necessary to sustain the organism than alcohol or tobacco; but taken in moderation in the absence of certain forms of disease, which we shall shortly consider, coffee forms an exceedingly pleasant beverage. Its effect upon the organism and special action on the central nervous system (psychical behavior), have been separately considered in the physiological part, where it is stated that coffee has no nutritive value, directly or indirectly.

There are, however, many conditions which limit or, according to our ideas, entirely forbid the use of coffee.

The first of these is childhood. No child should drink coffee before the age of puberty, and certainly not before the age of ten yeaes. Milk and soup are sufficient beverages. The necessity derived from habit does not exist in childhood, unless it has been produced by use from earliest infancy. Special nerve stimulation is entirely unnecessary. We are also firmly convinced that the early use of strong coffee (or of tea), is one of the many factors that produce a neuropathic disposition or develop such when inherited. In the same way we regard the use of coffee as inadmissable in the case of adults who suffer from so-called neuropathic tendency, nervousness, or pronounced nervous diseases (especially the so-called functional disease). Epileptics, hysterical persons, those suffering with severe chronic neuralgia and the like, should abstain entirely from this beverage.

We can assert that in not a few such cases great benefit has been derived from more rigid adherence to a course of diet, the chief characteristic of which was the absence of all so-called stimulants. Coffee should also be avoided in various diseases of the heart; namely, all deficiency of the valves, even when compensation has been established; in hypertrophy of the left ventricle, resulting from atrophic kidneys or strain, as well as the strictly functional, so-called nervous palpitation which occurs in various aetiological conditions.

The same applies to all individuals who suffer arterial fluxions to the head, so-called "congestion of the brain," and habitual epistaxis. In most chronic (and acute) affections of the stomach, also, coffee is deleterious and is properly entirely avoided. It is obvious that it should be avoided by all who regularly suffer any unpleasant effects, however trivial, from its use. Such effects are psychical excitement, great acceleration of the pulse, and the like. It has been sufficiently proved above that the prolonged use of too strong coffee produces decidedly injurious effects. The commonest of these are disturbance of the digestion, palpitation of the heart, marked nervous irritability, with simultaneous diminution of the capacity for mental labor. Strong black coffee is of direct medicinal use as a stimulant in collapse, in about the same conditions as alcohol in connection with which it is frequently given (coffee with rum or brandy), also in somnolence, sleep, or coma produced by stupefying poisons. It is thus used to counteract the narcotic effect of opium, and after large quantities of alcohol.

Coffee is further of use in hyperemesis, especially when this has been produced by emetics or alcohol. In the latter case vomiting may sometimes be prevented by coffee, even after nausea has begun. Coffee is a favorite popular remedy for diarrhœa, and indeed sometimes seems to

check this in acute intestinal catarrh proceeding from drenchings (as in rain). It is ineffective in other forms of diarrhœa.

The manner of this action is not clear; possibly the high temperature of the menstruum has the greatest share in it. This result, however, does not invariably occur, and not the slightest reliance can be placed on the constipating action of coffee.

As is well-known coffee (the infusion) is never ordered from the drug shop, but always from the kitchen.

2. *Chinese Tea.*—The substances known among us as green and black tea are obtained from the same plant, the tea-plant (thea Chinensis), and exhibit different colors because of the different methods of drying, and are of varying strength and excellence according to soil, climate and season.

The single alkaloid of tea is caffeine (before the entire chemical and physiological identity of the alkaloids of tea and coffee was known, the alkaloid of former was called theine).

Tea-leaves contain twice as much caffeine as coffee-beans. Tea also contains tannic acid, partly combined with the theine, and identical with the tannic acid of the oak, a lemon-yellow ethereal oil, which gives tea its smell and part of its taste, also vegetable albumen, salts and other unimportant ingredients. The following is the composition of 100 parts of dry tea (according to Stenhouse, Rochleder, Mulder and others): Caffeine, 1.8; albumen, 2.7; dextrin, 9.8; wax, 0,1; chlorophyll, 2.1; gum, 2.5; tannic acid, 15.7; ethereal oil, 0,7; extractives, 20.8; ash, 5.4; potassium salts, 3.1; iron, calcium and magnesia salts, 1.7.

As so-called black tea is dried at a higher temperature than green, it contains less ethereal oil. There is no difference in the quantities of caffeine in the two.

Physiological Action.—In addition to caffeine, the most active constituents are ethereal oil and tannic acid. The latter does not occur in the solution to an important degree, nor is its taste noticed unless the leaves have been boiled. The action of the pure ethereal oil has not yet been investigated; we cannot, therefore, clearly separate its effects from that of caffeine, in the case of tea. The percentage of caffeine in tea-leaves is indeed twice as great as that in coffee berries, but this difference is compensated by the fact that to make a beverage of the proper strength requires but half as much tea as coffee. The statement of Leven that the alkaloid contained in coffee acts much stronger than that in tea is manifestly incorrect since the two are identical. Leven's error was caused by using a salt in one case and the pure alkaloid in the other.

The effect of tea on the body is, in general, the same as that of coffee. It produces increased quickness and activity of thought, banishes sleep, and induces comfortable sensations.

Moleschott claims to have noticed that tea stimulates the fancy less than coffee, so that mental work can be carried on with greater collection of ideas and more definite attention, and there is less liability of drifting into wild flights of thought. We have never observed this difference in ourselves.

A single immoderate dose of tea as of coffee produces sleeplessness, unusual bodily disquiet, tossing to and fro in bed, trembling, general feeling of uneasiness. Extreme doses cause difficulty in breathing, anxiety, and the trembling may become convulsive.

Regarding the dietary and therapeutic application of tea, we can refer *absolutely to what has been* said about coffee; whilst in our country the

former is considered more irritant than the latter, it is to be explained by the fact that people are generally far more accustomed to the use of coffee. In therapeutic use, the so-called diaphoretic effect of tea is chiefly due to the hot water; at all events, for this purpose linden and Elder blossom teas are on an average less injurious, especially when this remedy is used without regard to the presence of fever and inflammation.

Chinese tea is taken in the usual form of an ordinary infusion.

Paraguay Tea.—The tea extracted from the Ilex Paraguayensis leaves which in South America takes the place of Chinese tea on account of its effects, which resemble those of coffee, stands half way between coffee and tea, and contains one-half per cent caffeine, besides tannic acid. Its effects are said to be exactly like those of Chinese tea.

Guarana Paste.—The article made from the dried and powdered seed of the Paullina Sorbilis, a brown acid, bitter, paste (Pasta guarana), contains the most caffeine of all foods and remedies by five per cent, and besides this contains tannic acid. Although its physiological effects are not well known, there is no doubt, on account of its large proportion of caffeine, that its caffeine effects must be much more palpable than those of either coffee or tea.

Amongst ourselves guarana-paste is hardly ever used for therapeutic purposes. On the other hand, it is largely used in France, especially for blennorrhœas of the urinary organs, and for diarrhea on the one hand, and for neuralgia, particularly for migraine, on the other hand. Caffeine renders this remedy entirely superfluous. The best form for administration is in powder in doses of 0.5 to 2.0.

THEOBROMINE.

The alkaloid theobromine, $C_7H_8N_4O_2 = C_5H_2(CH_3)_2N_4O_2$, is produced from the cocoa-bean (Semina Cacao, of the chocolate tree, Theobroma Cacao), and is closely related to caffeine, and may be regarded as a methylized derivative of Xanthine (Dimethylxanthin); it is a white, crystalline, slightly bitter powder, and dissolves slightly in water, alcohol, and ether.

PHYSIOLOGICAL EFFECT.

According to Mitscherlich, and, later to Bennett, Theobromine is similar in its effects to caffeine, only weaker. According to the former, a fatal dose for frogs is 0 05 grm.; for pigeons, 0.5 grm.; for rabbits, 1.0 grm.

Mitscherlich describes the poisonous symptoms as follows: Frogs, which swell immensely through expansion of the lungs, die from slow absorption, with appearances of paralysis of the spinal cord and vagus (?). Buchheim and Eisenmenger found the muscular curve caused by theobromine so similar to that of caffeine, that they could readily be mistaken for each other.

In rabbits, there appears gnashing of the teeth, falling respiration and temperature, increasing frequency of the pulsation of the heart, which becomes weaker and weaker,

and, when the absorption is slow, gradual torpor, and rapid convulsions. Secretion and excretion are not changed. After death the intestinal peristaltic motion and the sensitiveness of the muscles continues for a long time. The urine always presents theobromine in these experiments.

Further detailed researches are desirable. Theobromine is not used therapeutically, but an article of food containing theobromine is used largely, namely:

Chocolate, Cocoa.—All the different kinds of chocolate have as a basis of their composition the powdered cocoa-bean (Semina Cacao). The following is the percentage of their chief component parts :

Theobromine	0.5	to 1.0	per cent.
Fat (Cocoa butter)	30.0	to 50.0	"
Starch-flour	10.0	to 20.0	"
Albumen	10.0	to 15.0	"
Salts	2.9	to 3.0	"
Gum	0 5	to 1.0	"
Water	4.0	to 6.0	"

Extraordinarily different results have been obtained by different observers.

Physiological Effect.—This has been very little studied. Besides the theobromine-effect, similar to that of caffeine, we observe the nutritive qualities of starch, and perhaps also of the oil, which, however, is not well borne by the stomach without a liberal addition of spices ; but even without these cocoa can be as safely used when the oil has been extracted, as can spiced chocolate.

Dietary Use.—When the amount of theobromine contained in chocolate is considered, its use is limited the same as that of tea and coffee. The same applies to cocoa, from which the oil has been extracted, and to the so-called "Sanitary chocolate," because these both still contain theobromine. It is not used directly for medical purposes; it simply is a pleasant, savory article of food, particularly when spices are added, which certainly has an advantage over coffee and tea as an article of direct nourishment, and therefore as chocolate cakes are easily carried, it is very often taken along for walking tours, marches, and such excursions.

COCAINE.

Cocaine, $C_{17}H_{21}NO_4$ is the chief alkaloid of the coca-leaves of Erythroxylon coca (Erythroxyleæ), which crystallizes in large colorless prisms, and when heated with muriatic acid resolves itself in benzoic acid, methylic alcohol, and a new alkaloid, Ecgonin, $C_9H_{15}NO_3$. Coca-leaves, at the very most, contain but 0.2 per cent of cocain.

PHYSIOLOGICAL EFFECT.

Cocaine is an inebriating and stupefying alkaloid (Moréno, Schroff, Danini, Anrep).

Local Effects.—Injections under the skin, as well as ex-

ternal application to the mucous membrane, as, for instance, that of the tongue, cause local anæsthesia and analgesia. Fifteen minutes after the application, Anrep could not distinguish sugar, salt and acids from one another on that spot; neither could the prick of a needle be felt there; whilst the other side of the tongue, to which the application had not been made, acted normally. The length of this numbness, or torpor, varied from 25 to 100 minutes.

General Effects.—In cold-blooded, as well as in warm-blooded animals, the central nervous system especially is attacked. The former are immediately paralyzed, and the latter become excited to a high degree and, only later on, weakened. The observations of Anrep, with regard to dogs, which we (Rossbach) also share, leave no doubt that their psychical functions become materially influenced. A docile dog, in normal condition, became entirely changed after being poisoned with cocaine (he weighed 1 kilo, and 0,01 was given him). Almost immediately after the injection, he would not stay for a moment in the same place, but danced on his hind-legs, with his fore-feet held up in the air, 'round and 'round his master. All the muscles of his body worked incessantly, and he wagged his tail constantly. The abdominal and respiratory muscles were in constant play. At the same time, all these movements, which embraced the whole body, had nothing of the nature of a spasm about them, but the dog appeared by his actions just as if he had been suddenly moved by some great gladness, such as encountering once more his long-lost master. The expression of his face, and his entire behavior, displayed only joyful exaltation, and not the slightest symptom of pain. The peculiarity of the cocaine condition consists in that the dog did not merely keep up these movements for a short time, like one that had experienced a sudden pleasure, but maintained it for hours, and did not stay quiet for a second, as long as he was let do as he pleased. When a hand was placed on his head, or on his back, he could restrain himself and keep quiet, and then only the continuous heavy breathing betrayed his excited condition. That state lasted from one to three hours; then he became quieter and, eventually, normal, without showing signs of fatigue—in fact, he was quite fresh, and apparently in good spirits. When larger doses are given (0.015 to the kilo), the effect on the dog is far more violent. He suddenly changes his physiognomy; no longer knows

his master; commences to be restless; howls plaintively, and trembles. He starts at every sound; the trembling increases, and he carries his tail between his legs; he swings his head like a pendulum, gradually faster and faster; at the same time, his timidity increases. Every now and then new groups of muscles begin to twitch, so that, at last, this dog, who remains all the time in the same spot, adds to the pendulum movement of the head a snake-like motion of the whole body, in metrical rhythm. At the same time, the breathing is hurried; the pupils dilate; the skin hot, and the buccal mucous membranes dry. After this condition lasts about fifteen minutes, the picture suddenly changes, and the psychical condition is converted into the reverse. Fear and terror cease, and a boisterous hilarity supercedes them—the evidences of attachment are evinced in the most exalted manner. This second stage lasts about fifteen minutes, and a third array of complex symptoms ensues. As if enchanted, the dog jumps 'round and 'round, incessantly, in circles, about the observer. It is extremely difficult to call the dog away, not because he does not recognize the voice of his master, or that he does not wish to obey, but because, in spite of his best will, he cannot—he is held back by the nearest observer, as by an unseen power; one sees plainly how the dog struggles between the desire to follow the call, and the power, which forces him to remain on the same spot. At length, after constant coaxing, the animal succeeds, by the exertion of all his power, in freeing himself from the enchantment; then he rushes, with great joy and remarkable swiftness, to the one who called him, but at once commences to dance in a circle around him, in the same way as before—the same performance is sometimes repeated again and again. Altogether, these symptoms of poisoning last three to four hours; then the dog gradually becomes more quiet; the breathing, which before was labored, returns to its normal state; the high temperature of the skin becomes reduced; fatigue and sleepiness ensue. The sleep is tranquil. The mucous membranes become moist again, but the pupils remain dilated for some time. After a few hours, the animal is quite recovered; he is hungry and eats with a good appetite. When still larger doses are given (0.02 to the kilo), enormous psychical excitement of the motor apparatus is called forth, and there are evidences of weakness, especially of the muscles; at last, the animal can no longer stand;

it lies on its side, with the feet drawn up close to the body, and has difficulty in breathing; consciousness still exists. If one calls, it lifts its head, and looks plaintively at whoever calls it. Twenty minutes after the commencement of the poisoning, clonic spasms ensue, with a swimming movement of the hind-legs, sometimes also rolling spasms, with opisthotonos. The convulsions become more violent, consciousness is lost; the head is incessantly struck on the ground, and the whole body has not a moment's rest. This state lasts for an hour; then there are a few moments of rest; they last longer and longer, and, after three to four hours, gradual recovery sets in, but there remain for a long while sleepiness, want of appetite and a general indifference to everything. The individuality of the dog, of course, makes various changes in the conditions described.

Relations of the Various Organs.—The central nervous system is attacked in all its parts, not through arrest of circulation, but by a direct influence of the nerve-cells. As the symptoms show in the commencement, the gray substance of the cerebrum is attacked, so that extreme pyschic exaltation ensues. The simultaneous extraordinary labored breathing, the pendulum-like movements of the head, the clonic spasms, the difficulty in maintaining equilibrium, the swimming movements, the incessant and often rhythmical contraction of all of the muscles prove, though, that all the other nerve-centres, such as the eminentia quadrigenima, the cerebellum, the medulla oblongata, and the spinal cord are affected. With caffeine, cocaine, like caffeine, has its stage of excitement, almost invariably followed by complete restoration to the normal condition, and only after very large doses before the return to complete health, is there a state of weakness and lassitude. Strange to say, the few experiments that have been made upon human beings indicate but little of exhilaration and much of depression. Schroff found only after small doses an increase of the working power of the brain; after larger doses there was certainly an increase, but it was soon replaced by depression and sleep. Fronmüller speaks only of giddiness, delirium, buzzing in the ears, and sleep. Ploss mentions giddiness, and inclination to sleep. After what we observed with Anrep in all animals (rabbits, cats, dogs and pigeons), we believe that when small and medicinal doses are given to human beings, symptoms of excitement must ensue, and that the want of such experience in obser-

vations of the kind is caused by the very few instances in which such an experiment has been made.

The pupils become dilated in cases of local as well as general *application.* The breathing always becomes labored, and after large doses tremendously so. Often a quite peculiar type of breathing is observed—namely, total cessation of breathing, then deep and slow respiration, which becomes quicker and more superficial, until at last, after great difficulty, total stoppage of breathing again ensues. Very large doses cause a state of exceedingly great difficulty of breathing, and at last paralysis of the lungs.

Circulation.—Small doses do not affect the action of the heart; medicinal ones impede it, especially in dogs. The pulse beats three times as frequently as in the normal condition, but the pulse-beats do not become weaker. After very large doses the pulse-beats become exceedingly slow. The cardiac branches of the sympathetic become less irritable after small doses; after medium doses totally so, and permanently paralyzed, so that the hastened pulse must be attributed to paralysis of the fifth pair, as when atropine is used.

The blood pressure also acts as in atropine poisoning. After medium doses, rising ensues, and large doses produce rapid sinking of the same.

The temperature of the skin at first rises very much with animals; in the rectum at first a sinking of from 0.5 to 1.0° C. is often observed in the beginning; during the convulsions, though, a rise also takes place there.

The striped muscles do not become affected. The movements of the large as well as of the small intestines become more active. At first the intestines become quite pale; then ensue energetic peristaltic motions, lasting five to ten minutes. Then the vessels again expand, and the peristaltic motions become either very weak or they cease entirely. Large doses first produce increased peristaltic motion of short duration, followed by distention of the *intestinal* vessels, which become replete with venous blood.

The excretion of urine suffers material changes sometimes, but albumen and sugar are found in the urine only after convulsions of long duration.

There is a decrease in the secretion of saliva and of *mucous.* Death of warm-blooded animals from cocaine is caused by final respiratory paralysis, and the heart con-

tinues to beat for some time after general death has actually taken place.

Many extraordinary things have been told of the coca-leaf and its wonderful effects, and it gave rise to the opinion that it would prove a great article of economy. Anrep experimented to elicit whether cocaine possessed the same quality, but only on a rabbit. He found, though, that starvation ensued at about the same time with and without cocaine, and that the loss of bodily weight varied in both experiments within the same limits.

Therapeutic Application.—Thus far cocaïne has found no medical application, but on account of its extraordinary exciting effects on the nervous system, respiration, on the action of the heart, as well as for its local anæsthetic effect on the mucous membranes, it merits trial in a variety of diseases. The adult dose must be within the decigrammes.

ALIMENTS CONTAINING COCAÏNE.

Coca.—The coca-leaves (see above) contain, besides the cocaïne, another alkaloid called hygrin, which is, Woehter considers, physiologically inactive in rabbits.

Physiologicol Action.—Travellers report that cocaïne enables Indians (who chew the leaves mixed with lime) to bear fatigue very long, even with but insufficient nutrition (Tshudi). Gazean mentions the following partially contradictory statements in reference to the results of chewing coca: The flow of saliva is diminished, the sensibility of the mouth, throat and stomach are reduced, hunger is supported longer; but digestion is accelerated, and the quantity of urine increased; no narcosis.

Mantegezza observed that by the use of small doses excitation of digestion was provoked; middling doses irritated the nervous system and increased muscular power; while large doses increased respiration and the action of the heart, and also produced fever, hallucinations, and delirium.

Schroff observed no improvement of his digestion from the use of 9.0 grm. of an excellent preparation of coca, but after the use of larger doses he felt an unusual excitation of his vascular system and of the functions of the brain, with increased muscular power, and of physical and mental cœnæsthesis. We must await more exact experiments before we can form an opinion, but the actions of cocaïne and coca certainly do not seem to be identical.

Some experiments have been made, but no very reliable results for the medical use of coca-leaves have been as yet obtained. They are recommended in mercantile advertisements for all varieties of evils.

THE ALKALOIDS OF OPIUM: MORPHINE, CODEINE, NARCOCEÏNE, PAPAVERINE, NARCOTINE, THEBAÏNE.

We will first consider the physiological action and medical uses *of the chemically* pure and more important alkaloids *of opium, and* opium alone afterwards. Opium, the

juice which exudes from and dries in cuts on the green heads of the garden poppy, *papaver somniferum*, like every juice of plants, is a mixture of divers chemical substances; its physiological active parts almost all belong to the group of alkaloids, of which there are about twenty different ones found in opium.

The alkaloids of opium which are most known are: Morphine, codeine, papaverine, narcotine, narcëine, thebaïne, porphyroxine, opianine, metamorphine, cryptopine, hydrocotarnine, rhöardine, lanthopine, laudanine, landauosine, protopine, codamine, meconidine, meconoiosine, gnoscopine.

Besides these some acids are found in opium, of which the most important is meconic acid, with which most of the alkaloids mentioned form meconic salts. Meconic acid alone exercises but few unimportant physiological actions. Very few of these alkaloids have thus far been subjected to physiological investigation, therefore only these few can be discussed here; they have almost all special narcotic actions.

MORPHINE.

Morphine, or morphium, $C_{17}H_{19}NO_3+H_2O$, if crystallized from alcohol, forms small, colorless, brilliant prisms of a slightly bitter taste and alkaline reaction. They dissolve in 500 parts of boiling, and in 1,000 parts of cold water; and do not dissolve in ether, chloroform, nor benzole, but dissolve easily in alcohol. The contents of morphine in opium varies between 5 to 20 per cent. The easier soluble salts are preferred for medical use; such as the hydrochlorate of morphine, $C_{17}H_{19}NO_3HCl+3H_2O$, which dissolves in 16 to 20 parts of cold water, and the sulphate and acetate of morphine.

PHYSIOLOGICAL ACTION.

Morphine is certainly the most important alkaloid of opium, because opium contains much more of it than of all other alkaloids, and it is its most active principle as well as the one which exercises its best practical physiological action.

The poisonous action of morphine is very different in different animals. Frogs are very often attacked by tetanus as after strychnine. Birds are the most indifferent of all warm-blooded animals to its action, and pigeons and chickens digest doses which would kill an adult human being without any special toxic symptoms. Subcutaneous injections of as much as 0.1 grm. and 0.5 per oram exercised but little effect. Rabbits, dogs, and cats may take

larger doses than would kill a man, to merely produce sleep. We injected doses of 1.0 grm. into the veins of many dogs of medium size without producing sopor. In dogs large injections are required, for if they be divided into several doses the narcotic effect is not produced. Human beings are much more susceptible to its influence than any other animal, for which reason no proper conclusions can be made from experiments on brutes. Individuality is of great influence in experiments on animals and human beings, as there is a wide divergence in the quantities of morphine which poison or kill.

Children are especially sensitive to morphine up to their fifth year; some have died upon taking 0.001 grm. of morphine, others recovered from much larger doses. We often see people who are not used to taking morphine grow excited and sleepless from a dose of morphine which puts others into a deep sleep: nervous and feeble persons are apt to grow excited, while vigorous people are narcotised more readily.

The dose that proves fatal to persons who are not accustomed to its use varies widely; some adults have died from 0.06 grm. morphine, while in others 1.0 grm. produced severe toxic symptoms, which were followed by complete recovery even when the morphine was not vomited before it was absorbed.

As it is thus impossible to foretell the fatal dose, it is clearly necessary to always begin, especially in children, with very small doses, and to advance very cautiously until the desired effect is produced.

If people are accustomed to morphine, the conditions are very different; for as with other narcotic remedies, animals and human beings may gradually take larger doses. If 0.01 relieves pain or produces sleep in the beginning, a 100 times larger dose may be finally necessary to produce the same effect, as did the small dose at first. Even children become accustomed to large doses.

Morphine exercises a stronger hypnotic effect in the evening than it does in the morning.

Direct injections into the blood produce the quickest effect; 5 to 20 seconds after the injection we note dizziness, dyspnœa, great anxiety, and faintness; but without greater danger to life, than from any other form of application: in subcutaneous injections the action begins only after 5 to 10 minutes; when taken internally its action depends upon

whether the stomach is filled with food or not, and the effect is only seen ¾ to 1 hour afterwards. Absorption and general effects also appear after introduction per rectum.

Changes of Morphine in the Organism.—The intact skin does not absorb morphine, or any other alkaloid of opium. The mucous membrane of the stomach and the intestines absorbs it slowly, if taken internally. *Draggendorff* and *Kantzmann* found small quantities of morphine in the human stomach 15 hours after its application; in cats it was also found 15 to 18 hours afterwards, in the small intestines. Sometimes the whole quantity of morphine is not absorbed, as Draggendorff found small quantities of it in the excrements.

After absorption morphine was traced in the blood and in many organs, especially in the liver; it does not remain long in the body, however, but is quickly secreted with the urine, the greater part of it probably unchanged (Hilger, Draggendorff). Its excretion begins soon after it is taken, and concludes between twelve to fifty hours thereafter.

The slow absorption and rapid excretion partially explain how animal organisms grow so easily accustomed to morphine, and that its action, when taken internally, is not so sudden as in other poisons.

Phenomena of Acute Poisoning by Morphine.—The first symtoms of small doses (0.01 grm.) in man are usually those of excitement, greater mental and physical activity, insomnia, restless motions, sometimes even hallucinations; afterwards slight headache and obtunded sensorium, drowsiness and deep sleep, from which the subject, however, may be easily aroused.

The stage of excitement is very short, or does not set in at all after medium doses; narcosis begins soon and the deep sleep can, however, be easily interrupted; there are also nausea and vomiting, especially by a full stomach; desire to urinate, with difficult discharge, prickling of the skin and skin eruptions. After great doses (of 0.06 grm. and more) deep and prolonged sleep and finally perfect coma appears, with immobility, contracted pupils, slower, painful, often irregular respiration, retarded, irregular and diminished action of the heart and relaxed muscles; insensibility to pain, and finally the pupils do not act under the stimulus of light. This condition is sometimes recovered from; respiration, and the action of the heart improve, and an ap-

parently normal sleep comes on, followed by a return to consciousness, accompanied by weariness, headache, all possible nervous disorders, nausea, constipation, retention of urine and skin eruptions; or death results after the pulse and respiration grow weaker and weaker, the blood accumulates carbonic acid gas (Cyanosis), and finally the end is reached, with clonic and tonic convulsions probably produced by poisoning with carbonic acid gas, or sudden collapse may take the place of the foregoing.

The symptoms in animals are similar, but they require larger doses. It has been mentioned that frogs are often attacked by tetanus as a sympton of irritation. Dogs, which are put to sleep with difficulty after large doses, sometimes act like people strongly under the influence of alcohol. They tremble, totter, fall, drag their hind legs after them, and have a silly, torpid expression of the face. Otherwise they vomit as easily as human beings, and are just as insensible and severely paralyzed as they.

Chronic poisoning with morphine is seen often nowadays, in consequence of the extensive employment of continued subcutaneous injections of morphine. For a time such patients feel better and happier; but after the lapse of four to six months, more rarely after years, symptoms of disease appear, such as dry mouth, thirst, nausea, vomiting, constipation, sometimes difficulty of respiration, palpitation of the heart, retention of urine and difficulty in urinating; in graver cases, albuminuria, impotence, amenorrhœa, restlessness, insomnia, hallucinations, variable temper, hyperæsthesia, neuralgia, paræsthesia, tremor of the hands. Abstinence from morphium is not tolerated, and may lead to similar symptoms as alcoholism. Levinstein gives the name of *morphinismus* to this condition.

Action of Morphine on the Different Organs.—It is surprising that, in view of the enormous use of morphine, we possess so few reports of precise physiological experiments upon its action. But this may be explained by the fact that men who are very susceptible to the action of morphine cannot be experimented upon with all pharmacological methods, while animals do not long respond so readily to its action. Deductions from experiments on animals must evidently be made very cautiously.

Brain.—The mental symptoms of the use of morphine appear to indicate that the cells of the nerve-centres of the grey matter of the cerebrum are excited at first, then they

are depressed, and finally paralyzed. Witkowsky denies, as a result of his experiments on animals, especially frogs, that an increased irritability of the centres of the brain precede their paralysis. He says that excitement and peculiar restlessness are rare, and that they can be explained by the diminished action of the highest psychical centres, whose retarding influence on the nervous system loses its vigor and influence, and ceases totally in the end under the influence of morphine. He claims, furthermore, that the early disturbances of respiration and digestion easily cause restlessness. We do not agree with Witkowsky in this regard, because we observed insomnia when we took small doses of morphine for other reasons, although we always enjoyed good sleep before and afterwards. We observed the same in patients, who lost their sleep after small doses of morphine, and fell into a deep sleep when larger doses were given, and we cannot imagine that insomnia should be a symptom of diminished action of the highest psychical centres. Even if morphine plays such a prominent part in all hospitals and insane asylums in the treatment of conditions of excitement in women, and especially in hysterical women, this fact does not preclude morphine from exciting the same cerebral portions when small doses are employed while larger doses may paralyze them, as so many other narcotic remedies do.

The brain is often found hyperæmic, and again, anæmic, during the sleep caused by morphine, which proves that this sleep cannot be caused by changes in the circulation. Probably a direct change of the substance of the cells of the nerve-centres, brought about by morphine, is the cause of it. Whether the morphine be held chemically by the albuminoids, as we saw in dead albumen, or whether it is only an action by contact, is dissentible, but the changes must be lasting, else sleep would cease sooner, as also the psychical disturbances of morphia-eaters, which last a long while even after no morphine is taken, proving an interruption in the nutrition of the brain. Dragendorff could not find morphine thus far in the brain of such people or animals, but it may yet be found. Binz compared three pieces of gray substance of the brain, of which he put one into a two per cent. solution of chloride of sodium, another into a solution of sulphate of atropia, and a third into a solution of sulphate of morphia. He *examined them* microscopically, and found that the cells of

the nerve-centres had clear, sharp borders, and were slightly clouded, the intermediate substance bright in the first two, whilst the piece which had been immersed in the morphine solution showed that its cells had sharp borders, the protoplasm was turbid, and the intermediate substance dark. Upon adding diluted acids he obtained appearances which recalled a process of coagulation. The greater darkness of the intermediate substance, in opposition to a normal preparation was seen even in a solution of morphine of 0.02 per cent. Binz found the same darkening of the grey substance in the action of other soporific remedies like chloral, chloroform, ether, but not by atropine, caffeine, camphor, or pyrogallic acid.

Certainly the nerve-centres of the brain are the first parts affected by morphine. The sensorium is impaired in man while reflex motions from the spinal cord are not yet markedly reduced. The fact is proven that those animals which have the largest brain are most easily affected by morphine. That amongst the highest animals —man—the most intelligent races, the Europeans, are narcotized more profoundly, while others merely become excited. That animals with little brain are not narcotized except by very large doses of morphine, while they are affected with symptoms of excitation of the spine up to tetanus (frogs) (*Buchheim*), but whether the intensity of the action depends only upon the quantity of the brain or upon qualitative differences is uncertain, but the latter is probable, especially in view of the fact that children are more easily affected by it than are adults.

The Spinal Cord is affected later than the brain, and is first irritated by small and medium doses. This irritation is especially clear in cold-blooded animals whose reflex irritability is increased even to tetanus, but is speedily exhausted, and this is also observed in warm-blooded animals and in human beings, in whom it manifests itself by increased sensitiveness, restlessness, nausea and vomiting. We see, therefore, that reflex action is increased (Cl. Barnard), when the sense of pain has almost ceased. Witkowski observed that reflex irritability in frogs always vanished for a time after a morphine convulsion, and then it returned after an interval of several seconds in the shape of an anomalous convulsive motion; the spinal cord is therefore not only easily excited as by other tetanic poisons, but it is also easily exhausted. Greater doses are required to

paralyze the spinal cord than to paralyse the sensorium, and the different parts of the spinal cord are also differently susceptible to its action.

The first effect is seen in the reflex nerve-centres. Animals and human beings can breathe regularly long after they are unconscious, and without reflex action, which proves the continuance of the irritability of the centres of respiration. But if these begin to fail in the progress of poisoning, and respiration begins to grow irregular, slower and weak, then the vasomotor centre is still excitable, which can be observed by the prompt increase of blood-pressure, which results upon gentle irritation (Rossbach and Schneider). We rendered dogs insensible and unconscious by injecting 0.01 of morphine into veins, so that the most painful operations did not cause a single convulsive motion and no change in the depressed respiration, while a prompt increase of blood-pressure was produced by feeble irritations to the ischiatic nerve. Respiration remains intact in animals and human beings for a long time; it is never accelerated by morphine, but if there is a change, it becomes slower because of a reduced irritability of the centres of respiration. Even when Gscheidlen injected morphine directly into the carotid, the frequency of respiration was diminished; according to Filehne it becomes intermittent in the beginning of the action of morphine, so that after intervals of 5 to 20 seconds—2 to 3 rather even respirations appeared, but were separated by small intervals.

The periodicity of respiration is equal to that of the blood-pressure. The intervals in respiration and the diminished blood-pressure are purely apnœic symptoms, caused by anæmia of the medulla oblongata in consequence of contraction of the blood-vessels. The lack of response to irritation by the centres of respiration may become so acute in severe cases of poisoning that respiration ceases entirely and death is the necessary result.

The certainty with which morphine, even in small doses, stops the disposition to cough produced by peripheric causes like laryngitis, ulcers, etc., proves that even the sensitive nerves of the larynx, trachea and lungs are influenced by the action of morphine, in reducing the irritability.

The Peripheral Nerves are less attacked than the nerve-centres, when morphine is taken internally; the sensitive

nerves of the skin are not affected in the slightest degree; the seat of sensibility in the brain is certainly paralysed long before the peripheral nerve is affected, which is proven by the long presence of reflex action in unconsciousness. When morphine is injected directly in the neighborhood of a sensitive nerve, so that the nerve itself is washed, particularly when a strong, concentrated solution is used, then we see symptoms of paralysis within its sphere before the brain is affected; the sense of feeling is dulled, pain is relieved, and afterwards ceases entirely in the region into which the injection is made, while feeling and pain on the corresponding other side of the body remain intact and consciousness is perfect. The faculty of conduction of the greater nerve-trunk is also reduced considerably if a part of it is exposed to subcutaneous injection of morphine (Lichtenfels Eulenburg).

The only exact experiments on the *motor nerves* were made by Gscheidlen, who found a considerable increase of the irritability first after small doses, but followed by a decrease of it which came on immediately after great doses; but could not produce a complete paralysis even when he employed very large doses. (Opposed to Albers). A normal nerve requires closer approach of secondary electric spiral to the primary one for the purpose of producing contraction of the muscles of the leg, the nearer the irritated point of the ischiatic nerve lies to the leg (Budge, Pflüger); but in morphine poisoning the opposite condition obtains, for the portions of nerve near the center, require much stronger induced shocks, to cause muscular contractions than do those which lie near to it. In warm-blooded animals, no matter in what stage of morphine poisoning we made our test, we could always produce muscular contractions by irritating the nerve that controlled them.

The Pupil is contracted in most people and animals almost during the whole action of morphine; for this reason morphine has often been accorded a place among the myotic drugs, but erroneously so. If morphine is put into the sac of the conjunctiva, no contraction is observed, and a very slight one in cats, which, however, is probably caused by the irritation of the injection; for the motility of the iris is perfectly preserved. We must, therefore, separate morphine from such remedies as *atropine, physostigimine,* which act directly on the pupil. Nor do we find contracted pupil *in the general action* of morphine in *all* animals, nor in all

persons, nor in all stages of the poisoning. Such an irregular symptom cannot be caused by a direct irritation or paralysis of any definite, much less of a peripheric organ, like in the regular results of atropine, etc.; it seems rather to be the result of complicated action in the centre, where, under certain conditions, a contraction is caused; probably morphine causes a contraction of the pupil by paralysis of such psychical centres which have a mydriatic influence (Cl. Bernard, Witkowski). At the same time that contraction of the pupil occurs spasm of accommodation is observed (Graefe).

The irritability of voluntary muscles remains perfectly intact, at least in frogs (Gscheidlen); nor do warm-blooded animals manifest any effects from it in this regard.

Organs of Circulation.—Small medicinal doses increase the number of pulsations in warm-blooded animals, either in consequence of an irritation of the nerve-centres which supply the motor muscles of the heart, or by diminished action of the centre of the vagus. Large doses produce, firstly, an acceleration of the pulsation, then a diminution. This diminution is caused in the beginning by an irritation of the retarding apparatus in the brain and heart; later on, these are paralysed, but the slow pulse remains, because the nerve-centres of the motor muscles of the heart are weakened. The heart certainly resists the influence of morphine as long and longer than any organ and can only be killed by very large doses, and only long after the death of the whole central nervous system.

Even when complete narcosis is produced by morphine in febrile conditions, the pulse is not reduced. (Witkowski).

The blood-pressure is not modified by small doses of morphine, and it is but inconsiderably depressed, frequently, though not always, superinducing noticeable increase of tension in warm-blooded animals. This is probably caused only by the pain from the insertion of the canula, and not by the morphine.

Larger and poisonous doses reduce the blood-pressure very inconsiderably in many animals and individuals; in others, rather strongly, evidently in consequence of a weakening of the vasomotor centre and consequent distension of the peripheral vessels.

The orbicularis muscles are not notably influenced; the *sympathetic also* retains its normal irritability.

This distension of the vessels presents itself in man in the

form of roseola, congestions in the direction of different organs, particularly towards the head. The feeling of ease after taking morphine, which many attribute to the distension of the vessels, should rather, as we have already stated, be ascribed to the suspension of the sensations which disturb the general sense of feeling (Bernard, Gcheidlen, Nussbaum, Binz, Witkowski). At any rate, no essential weakening of the circulation need be feared from the ordinary medicinal doses.

The applicability of morphine depends upon the fact that the organs of consciousness and of feeling are affected so easily, while the organs of respiration and circulation requisite for the sustenance of life, are affected so late, and comparatively inconsiderably.

There are exceptions, but mostly only in extant morbid changes in these vital organs.

The temperature is said to be elevated by small doses, and that poisonous ones immediately reduce it considerably; that it falls quicker in the cranium than in the rectum (Mendel). Manasseïn believes that the temperature depends solely upon the prevalent condition of circulation, that consequently it increases with the elevation of the blood-pressure and decreases with the decrease thereof; that it has no direct influence, as, for instance, quinine has, on the processes developed in the histiological elements; and that low organisms, decomposition and fermentation are not at all, or but slightly, influenced by it. The diminution of the red blood-corpuscles produced by morphine is said not to be due to a direct change in them, but to the decreased circulation of the blood in the organs, and a decreased supply of oxygen, wherefore the diminution of the blood-corpuscles is said to correspond with the decrease of temperature and with the profundity of the narcosis.

Slight febrile temperature is occasionally noticed after hypodermic injections of morphine, in consequence of local irritation. That the doses of morphine given during the course of febrile diseases have no influence on the temperture has already been stated.

Organs of Digestion.—Morphine taken internally causes a bitter taste, a dryness of the mouth in man; in dogs, however, a very copious secretion of saliva. This difference of effect may simply be due to the circumstance that the apparatus of reflex salivary action is only irritated in the *less sensitive dog*, while in sensitive man it is paralyzed.

It is probable that with certain doses, the irritation and consequent increased salivary action may have a contrary effect also on the dog, for in man also a temporary increase of saliva has been observed after taking small doses of morphine.

The nausea and vomiting which readily occur when morphine is taken on a full stomach are certainly the effect of morphine, and not attributable, as Pierce maintains, to an adulteration thereof with apomorphine.

Soon after the irritation paralysis of the sensory nerves of the stomach occurs, causing the feeling of hunger and pain in the stomach to cease, ordinary emetics to be ineffective after the administration of morphine, and to exercise a corrosive effect upon the gastro-enteric mucous membrane. Chronic catarrh of the stomach, after prolonged use of morphine, is caused by the disturbance of the secretion of gastric juice and the consequent abnormal digestion of food.

The statements of O. Nasse and Gscheidlen, that increased peristaltic action and increased irritability follow the injection of 0.025 grm. into a vein of a rabbit have caused considerable confusion, so that many authors flatly deny all constipating properties of morphine and attribute aperient effects to it, or that the constipation nevertheless noticed is ascribed by them to a decrease of irritability of the sensitive intestinal nerves in spite of the increased peristaltic action.

Our opinion, based on observations on man, is:

As most other nerves are first affected by morphine, this is at least most probable for the intestinal nerves, and this probability attains a certainty through the results of said observations.

However, the unquestionable correctness of the facts, frequently and easily substantiated, that the most violent colics superinduced by intestinal spasms, as well as painful diarrhea, tenesmus, all caused by a violent irritation of the intestines, can certainly be removed in man by means of morphine. This proves just as positively as Nasse's experiment on dogs, that a marked reduction of morbidly increased energy of the peristaltic motion at least—even complete intestinal rest—is the result of the secondary effect of smaller, or primary effect of larger doses of morphine.

Opium, as we have often seen, acts in a more reliable *and quicker* manner on these conditions, but morphine has *the same qualitative* effect; proportionately larger doses of

it are, however, required. We will give a more minute explanation of this difference between morphine and opium when we speak of the latter.

Its Modes of Excretion.—With an increase of temperature in the skin, itching sensations commence, and sometimes considerable perspiration will take place, with the appearance of veritable eruptions.

We have before detailed its influence on the secretion of saliva. It is generally understood that the secretions from the other larger and smaller glands of the alimentary canal, as the bile, etc., are decreased. After giving large doses we generally note a reduction of the quantity of urine, whether as a consequence of a decrease in the absorption of water, or through decrease of vascular pressure, remains unknown. This reduction shows itself in normal as well as in abnormal conditions of secretion, as, for instance, in polyuria.

In such circumstances we observe a reductive substance which seems to be sugar in human and animal urine.

C. Eckhard found that in healthy rabbits doses of 0.03 to 0.06 grammes of sulphate of morphine, when injected into the jugular vein, will, as a rule, produce marked diabetes within one or two hours; this always lasts three to four hours, sometimes longer. He demonstrated the presence of sugar by the use of Fehling's solution, with all precautions, and also by fermentation.

As a result of first exciting and then paralyzing the *musculus detrusor vesicæ*, commencement of the effects presents strangury and ends with retention of urine up to death.

Tissue Metamorphosis.—The excretion of nitrogen, during a brief period of the use of morphine (0.1 gramme pro die), is somewhat diminished in dogs. The excretion of carbonic acid rises in dogs and cats when the action of morphine is exciting; it falls when the action is soporific; it depends, therefore, on the activity of the muscles and not on any specific effect in the action of morphine (v. Boeck and Bauer). In men, the arresting action of morphine on tissue metamorphosis is certainly much more marked than in dogs, which are not very susceptible to morphine. Kratschmer observed a diabetic patient in whom, at first, opium (which contained 13 per cent of morphine), and afterwards morphine itself, caused such a reduction in the excretion of sugar that it eventually disappeared altogether, and while

the secretion of urea decreased also, the patient gained more than 2 kilos in weight.

Emaciation and rapidly-failing strength in chronic morphine intoxication is merely the result of the loss of appetite and insufficient feeding, and not caused by abnormally increased changes in the substance of the body.

Therapeutics.—"This drug is so indispensable and useful a tool in the hands of a dexterous and experienced physician that medicine would be imperfect and weak without it, for he who understands its use will effect more by it than can be expected from any other remedy. He who knows it only as a soporific and anodyne, and merely strives to combat diarrhea with it, must be very inexperienced, and know very little of its powers, as it can be made use of in very many other conditions, and constitutes one of the strongest and most tonic means, yes, even a panacea, such as has not hitherto been found in nature."

No less a man than Sydenham is the author of these ideas. In truth, one might yet to-day unquestionably—considering its frequent indications and extensive application—declare morphine the most important and irreplaceable of all drugs. Because of this great importance in practice, we think that a more detailed description of those cases to which its use is properly adapted seems not only allowable but imperatively required.

Recently it has become more and more customary in practice to use morphine in place of opium and its preparations; a proceeding which appears, of course, wholly justifiable. Morphine actually meets nearly all indications of opium, much more surely, and, besides, it is a pure preparation, whereas opium is very uncertain, because of the variable amount of alkaloids, especially morphine, it contains. Our discussion therefore will be exclusively devoted to morphine. The few cases where opium is actually more efficient, or is preferred by habit and custom to morphine, will be separately spoken of hereafter.

There is scarcely any morbid affection in which this remedy, of such powerful therapeutic action, has not been tried. We cannot name them all here. But it is also difficult to gather all its indications under general points of view. An exact analysis of all individual conditions in which experience has shown morphine as most powerful teaches us that in these cases the favorable result must be attributed to a decrease of the excitability either of the

brain or of the spinal chord or of the peripheral nerves. The reverse action of morphine, that is the exciting one, is scarcely ever called into play; on the contrary, we endeavor to avoid it as much as possible. The general indications for the use of morphine would be the following:

Exalted activity of the brain and the sensory nerves (it is used less in affections of the motor nerves); conditions, also, in which success may be obtained by a decrease of even the normal activity of the brain (by inducing sleep) or of the sensory nerves. Yet, it must be strongly urged that we should not always resort to the application of morphine where such indications exist, as there are circumstances in which its use must be a limited one or must be entirely avoided.

Insomnia.—Since olden times opiates are the soporifics most employed, and they, indeed, surpass all the others, with the exception of chloral, which is often, but not always, more powerful in inducing sleep, but stands far behind morphine, in being only hypnotic, but not anodyne. Morphine causes sleep in various ways: firstly, by abating the pain which makes sleep impossible; it is, therefore, indicated as an hypnotic in all cases, if at all compatible with the condition that creates the pain; secondly, it creates sleep directly by its action on the brain; it is, therefore, applied in protracted chronic illness, in phthisis and other diseases; lastly, we observe that feelings of oppression, præcordial anxiety as it occurs in general dropsy, are abated by morphine, and then sleep ensues (compare, farther on, diseases of the heart). Of the application of morphine as an hypnotic in acute febrile diseases, when insomnia is caused by a high degree of fever, we shall speak hereafter. As to the appearance of sleep, we have mentioned that its production is more probable if the remedy is given in the evening, while its action is much less certain and less enduring and also requires larger doses if administered during the day. The required dose must be found for some individuals; ordinarily, it will be expedient to commence with a small one (0.005 to 0.007 gramme), and gradually to increase it until the desired effect is attained.

Chloral, though it brings about sleep quicker and more energetically than morphine, sometimes fails, when morphine will again be efficient, and, at the same time, it is an anodyne. Morphine generally exercises less of a soporific *effect on nervous,* excitable individuals, and then is often

excelled by bromide of potash. Its value is not diminished by this. The only important drawback in its *continued* use is the necessity of increasing the doses and the danger of morphine poisoning. As to the application of morphine in aid of chloroform compare the latter.

Mental Alienation.—Morphine (or opium) has been long used in psychical disorders, and in former times more extensively than now. Its application subsequently became more limited, and the introduction of chloral seemed temporarily to put it entirely into the background; but in latter years a revulsion took place; chloral is being much less used in psychiatric therapeutics, and morphine again came to the front.

There is a rather general consent as to its usefulness in active melancholia when the melancholic disorder is accompanied by restlessness and excitement; yet, it frequently acts well in some other forms of mental disease, in mania, in hysterics, in hypochondriacal and puerperal alienations, even in downright mental weakness.

The existence of sensitive hyperæsthesia with enhanced reflex irritability, both taken in the widest sense, have been accepted as indications for morphine (Schuele).

The old controversy, whether morphine or opium is preferable, seems to be decided in favor of the former. Its internal utility cannot be doubted; yet, hypodermic application has undeniable advantages over other means.

The method consists either in prescribing powerful doses to fulfil a certain single indication, as, for instance, to prevent a threatening paroxysm or to induce sleep; or in the gradual increase of smaller doses until rest is enforced. The latter mode of treatment was first developed into a systematic treatment by Schuele, with hypodermic injections, and has afterwards been carried still farther by Wolff and Voisin, both of whom praise it highly.

According to Wolff, these injections are most efficient if made anteriorly and laterally in the neck (in the neighborhood of the vasomotor centre) in large doses (0.02 to 0.08). Small doses only excite the restless patient still more. The pulse must guide us, "with paralytic symptoms of the vasomotor nerves, with pulsus tardus," that is, generally, in old individuals, the commencement should be with small doses (0.07 to 0.01); with a pulse of an opposite description, *in younger persons*, generally, larger ones are required. *General paralysis* of the insane demands particular cau-

tion. The general contra-indications to opiates which we shall point out later must be considered, and treatment must be adapted to the individual, avoiding, also, the creating an appetite for morphine.

Deliria.—As in acute inflammatory affections, the use of morphine in delirium requires a careful individual selection. *Delirium potatorum* has been extensively treated by morphine, and many authors consider the remedy indispensable. Enormous doses have been given until sleep ensued, that being the desideratum to be obtained at any price. Experience teaches the following: small doses will frequently create excitement, and large ones, if they act at all, produce a comatose state, from which the patient generally awakes unrefreshed, and inclined to relapses. If delirium tremens is complicated with an acute inflammatory process, morphine acts rather unfavorably on it. A goodly number of different statistical reports prove that the mortality after the use of morphine is neither small nor smaller than with other remedies. So that recently the conviction became general that delirium tremens takes the best course with an expectant dietetic treatment, and that this shows the most favorable results (L. Meyer et al.). It seems evident that morphine may be dispensed with in this affection; if it is to be used, it will yield the best results in cases that are not complicated with a feverish, inflammatory state.

The question of its use has besides lost much in importance since chloral has been introduced. It deserves to be noted that opium is considered of better action than morphine. In the deliria of the febrile acme in acute inflammatory disease, morphine should be given only exceptionally. This holds good also in typhus and the acute exanthematic fevers, though, with our present improved methods of antiseptic treatment, the delirium of fevers rarely demands special treatment. But in the delirium of inanition morphine acts excellently.

When after the critical fall of temperature in pneumonia, erysipelas or relapsing fever with a normal or retarded pulse set in, the patient becomes delirious in consequence of cerebral anæmia, morphine and a tonic and stimulants are indicated (wine, good nourishment). We know that such delirium of inanition may occur in the course of any protracted febrile illness, as in typhus abdominalis, and even in chronic diseases, phthisical conditions, carcinoma, cachexia, etc.

Neuralgias.—Of all anodynes in practical use, morphine stands decidedly first and irreplaceable in the assuaging of neuralgic pains. It is the unique remedy when all radical cure fails, to give the patient rest for a time at least. Since the introduction of hypodermic injections this usefulness of morphine became yet more marked. A direct cure of neuralgia is seldom effected by it, though in fresh or "idiopathic" cases without known aetiology after a few injections and without other remedies complete success may be obtained. It cannot be contended that any particular form of neuralgia is benefited more than others; it is irrelevant to the palliative anodyne effect whichever nerves are attacked; it is also equally immaterial what caused the attack, and lastly it regards no difference between peripheral or central origin of neuralgia. Here, too, hypodermic application has superseded internal use, and justly so, because of the possible local effects obtained by reaching the peripheral sensitive nerves directly. There is an advantage, it seems, in making the injections not only in the course of the attacked nerve, but also at points that are particularly painful on pressure (Valleix's pressure points). We insist, however, on moderation and precaution in this mode of treating neuralgia, as frequently cases occur in which, a radical cure being impossible, an immoderate application of the alkaloid has brought about chronic morphine disease; occasionally a well-timed stop and a temporary discontinuance of the drug is required.

Pain.—Besides for neuralgia proper, morphine is also the common remedy for every kind of pain, which nothing else soothes as well; and, given under proper circumstances, it is the only consolation to many incurables; and one might have to give up practising medicine without it.

The leading indications for its use when pain is caused by acute inflammation we will point out later on. As to chronic painful affections, they are almost invariably benefited, even if they resist all radical treatment. Amongst these are a number of surgical diseases, of which, as we cannot enumerate all, we name only carcinoma and painful lithiasis. It is the best remedy to ease agony or make death painless. In gastralgia, which appears as a symptom of anatomical lesions (carcinoma, ulceration), morphine is also the most valuable drug, and its internal use *seems to be no less* prompt than subcutaneous application.

Gerhardt and Ziemssen warn us not to carry its use too far in *ulcus ventriculi*, but to confine it to meet only actually severe pain, as patients whose painful sensations have been completely subdued are apt to become negligent in observing proper dietetic and therapeutic rules. Of small or even absolutely no value is morphine in the gastralgia of chlorosis, the same in hysterical gastralgia, neuralgic affections of hysterics being generally little controlled by it. The gastric pains in acute and especially toxic gastritis, often require its use besides the ordinary treatment. Enteralgia, or colic, does not always demand it, as it is often checked by direct treatment of the cause, though it often happens that opium may be given for the latter. Biermer's rule to treat all intestinal pains with opiates to avoid other therapeutical procedures which might favor the perforation of a latent ulcer in the vermiform process, of which the pain is a symptom, may be considered harmless. It can, however, obtain only in those cases where the nature and cause of such pains is doubtful. In painters' colic morphine plays an important part. Reliable observers confirm its usefulness, particularly in severe cases where there is much pain.

Tanquerel has treated a number of cases of lead-colic exclusively with morphine and eulogizes it. It not only removes pain, but instead of increasing constipation it facilitates discharge from the bowels by checking the spasms. In those severe colicky pains that accompany the passage of gall-stones and kidney-stones (hepatalgia and nephralgia) morphine cannot be spared.

Convulsions.—In tetanus morphine still holds a place amongst the many remedies that are recommended; however, it yields more readily to chloral. We only mention that it often acts only after a venæsection, especially in robust individuals. Hypodermic injections are very valuable in certain forms of reflex spasms, as in blepharo-spasmus (von Graefe) that appears in the course of corneitis, which yields at certain "points of pressure." All observers concur in the opinion that morphine is useless in epilepsy; sometimes it will, for a while, diminish the frequency of the attacks, but all proof is wanting that it ever cured the disease. It might yet be useful in cases of true reflex epilepsy caused by local irritation in the course of a sensitive nerve (hypodermically). Still less proven is its *value in chorea.* Like many other drugs it has been tried

in hydrophobia, where it is little efficient; but injections may induce temporary rest. Morphine is widely used to subdue the spastic pains in labor, especially when they amount to tetanus uteri. The doses must then be sufficiently large. It is evident that morphine is generally less useful in spasms than in neuralgia, and that its value is greatest in disorders of the motor nerves, when it gains an influence on the sensory nerves, by which the motors can be controlled; that is in cases of distinct reflex spasms.

Acute Inflammatory Processes.—Pain and insomnia during these processes seem often to indicate morphine. Numberless experiences of the best observers demonstrate, however, that, as a rule, in the acute feverish state, its use should be prohibited. Firstly, it often happens that the desired effect is not gained at all, the patient becomes still more restless, and there is this drawback, that by killing the pain we lose a standard by which to measure the development of the local affections; as pain does not cease in consequence of their arrest by an antiphlogistic treatment but only disappears, while the inflammatory process may continue unchecked during this deceptive improvement. From this standpoint we must judge the abuse of morphine so often practised in typhus, pneumonia, pleurisy, acute bronchitis, and many other febrile conditions. In diseases of the respiratory organs morphine is often used to check painful cough; but what we have just said in regard to pain generally applies here as well. The question whether morphine may not even cause an increase of the fever temperature we have not touched upon; that question still awaits a methodical, fundamental discussion. Personal experience incline us to discard scruples in this regard. We never made an observation that convinced us that morphine creates any appreciable elevation of temperature.

There are particular conditions that form an exception to the general rules for the use of morphine, and in consideration of the high practical value which the question possesses at the bedside, whether morphine may be given in a case of acute fever, we feel justified in drawing a sketch of the rules which have been laid down by the best observers during the last two centuries. Though this question is less urgent to-day, since we successfully combat many affections that were formerly treated by opiates, with chloral, quinine, *salicylic acid and* the cold bath, it is still a very important *practical question.*

As to typhus, Sydenham's rules still hold good; all unprejudiced observers of recent times have confirmed their practical value (Hoffman, Cullen, Holl, P. Frank, Reil, Graves, Watson, Griesinger, Traube, Liebermeister and others). There are two symptoms which may particularly indicate opiates in typhoid fever, viz.: violent diarrhea and delirium, excitement, and insomnia. Generally, diarrhea must be combated by other means (tannic acid, etc.), as in high fever, with excitement, and especially when there is stupor, opium is said to be noxious; but when the discharges from the bowels directly endanger life, and cannot be relieved otherwise, or when intestinal hemorrhage sets in, opium should be tried, and in such cases is deemed superior to morphine. Peritonitis, from perforation of the intestine, which may also demand the application of morphine, we will consider hereafter. From personal experiences we may say that we think morphine (opium) the most reliable remedy in typhoid fever, and we have administered it with excellent results even in very high fever and when the sensorium was greatly affected, though we combined its use with energetic antipyretic treatment. It is certainly the best remedy to procure intestinal rest in bleeding from the bowels.

The method in which it is employed is of the utmost importance in delirium or excitement. As long as there is a rise of the fever or when it culminates, when the face is flushed, the arteries tense, and the head aching, morphine is decidedly hurtful, and the same may be said when combined with febrile symptoms and the delirium is not active, but of a somnolent condition and a "mussitant delirious talk" exists. As soon, however, as towards the end of the second week or later (Sydenham fixes the twelfth to fourteenth day) the skin becomes cooler, the temperature falls off, the face begins to look pale, either with previous anæmia or by the ravages of the fever, when the pulse is still accelerated but weaker, and when great excitement and sleeplessness exist, then morphine in combination with wine and good nourishment becomes very effectual. Under such conditions it may be observed that a strong dose of "poppy juice" (as Reil wrote) will retard the pulse.

Whether in these cases one large or several small doses are to be given is a question of great importance. The majority of observers recommend the former, but Latham has well pointed out that too high a dose would easily bring

eternal sleep to such patients. We consider that, in face of the powerful action of morphine on anæmic persons in general, the greatest possible precaution is necessary and that small doses are almost imperative.

Opium (which means morphine) played a great part in the treatment of *malaria intermittens* before quinine became known; at present its use is restricted to those cases of slight or moderate severity in which quinine by itself is not tolerated by the patient's stomach, but is vomited when uncombined with the other drug.

Early and recent observers, on the other hand (Stoll, P. Frank, Reil, Griesinger, for example) with few exceptions (Werlhof) agree in the opinion that opiates are necessary in severe, pernicious forms of intermittents, when the attack exhibits great chill and disquiet, delirium and marked fever. For this purpose quinine is combined with opium (0.05 to 0.1 pro dosi), usually in substance. It is also useful in obstinate forms and (according to Reil) in cases where the attack ceases without perspiration. On the other hand it must be remarked that great care should be taken, in the use of opiates in pronounced algid forms of the disease. Morphine may be or may seem to be indicated by several symptoms occurring in the course of croupous pneumonia and pleuro-pneumonia. These symptoms are: delirium with sleeplessness, pain, cough, and dyspnœa, especially combined with the last two. If delirium exists in connection with high fever and is not caused by alcoholism, if the patients are vigorous when the radial artery is tense, the face turgescent, antipyretic remedies, not morphine, are called for. For the "stitches" of pleurisy, local bleeding, ice bags and cataplasms are in place, but hasty injections are not.

But in weak, anæmic persons or those of unusual nervous sensibility, in cases where energetic antipyretic treatment is not indicated and antiphlogistic measures cannot be borne, when prolonged sleeplessness, continual inclination to cough and violent pain are present, morphine not only may be, but even must be employed. In these cases it is most truly beneficial. The rules just given for pleuro-pneumonia hold also for simple pleuritis and acute bronchitis. Morphine was formerly, for the most part, stricken from the list of remedies in acute inflammatory affections of the central nervous system, especially in cerebral and spinal meningitis. Still in the course of these diseases conditions arise

which not only permit but demand this remedy, as Hope, Graves, and more recently Hasse, Leyden and others have pointed out. P. Frank and Stoll used it in the "asthenic" forms of these inflammations. In all cases morphine should only be employed after antiphlogistic treatment, but when after sufficient employment of these means violent headache continues, robbing the patient of sleep by day and night and keeping him in the greatest disquiet, morphine frequently exercises a surprisingly beneficial effect, not only on the headache but on the whole course of the disease. Again, stimulants and morphine must be used when the patient is recovering after the passage of the primary inflammatory symptoms that appear in a state of collapse after exhausting blood-letting, when the skin is pale and cool, the pulse accelerated and delirium (now the delirium of inanition) has again set in. In acute peritonitis the opium treatment was formerly urgently recommended by English authors (Graves, Stokes) whose observations have been confirmed by many others. In mild atypical forms, also in perityphlitis, recovery sometimes takes place without the use of opiates, though the authors mentioned and others, for instance Volz and Biermer, highly recommend it in all cases in order to bring the bowels to rest and to render the healing of the perforations possible.

In diffuse perforative peritonitis, on the other hand, morphine is always decidedly and urgently required. Its use here, indeed, has the after-effects mentioned in connection with inflammations in general, and the additional effect of often increasing meteorism. Still the extraordinary pain, so wearing on the patient, can be allayed by no other means, and morphine further fulfils a causal indication, by the reduction of the peristaltic action, which alone renders the closure of the perforations possible. The diffuse peritonitis which occurs in a certain form of puerperal fever (phlegmonous or parenchymatous), caused by an extension of the process of inflammation of the connective tissue, from the uterus to the peritoneum, demands, above all, strong, antiphlogistic treatment, but in addition opiates are indicated to restrict the peristaltic action, also when there is continued pain and sleeplessness. For diarrhœa and ileus we refer to opium.

In *acute articular rheumatism* the salicylic acid treatment of to-day enables us to almost entirely dispense with morphine; *but, occasionally, in* very acute pain, a dose of morphine

becomes necessary. The earlier views on the treatment of acute polyarthritis with opium, are of no import now.

In *acute attacks of gout* the experience of most observers (Garrod, Cullen, and others) agrees in showing that morphine should be avoided, and used only in exceptional cases when unusally severe pain keeps the patient in a state of violent excitement. We cannot, of course, here describe all acute febrile affections and their appropriate treatment with morphine. We have presented only the treatment of some of the most important forms. Still we think that the above remarks will suffice to give a point of departure for practical procedure in other cases.

Morphine often becomes a necessary remedy in *sub-acute inflammatory processes, with hectic fever* (in suppurations, pulmonary phthisis), when there is nervous excitement and continual sleeplessness (besides the possible indication for this remedy by pain or coughing). Patients of this kind cannot exist without it.

Diseases of the Respiratory Apparatus.—Pain and cough are the two symptoms for which morphine is given in these diseases.

It is shown above that when these are due to an acute febrile affection, the use of morphine is only permissible under certain circumstances. In chronic disease the pain is seldom very great, whence in this the inclination to cough is the only symptom indicating the use of morphine —but only on one condition. If the violent irritation which produces the cough is maintained by profuse secretion, morphine, like all so-called narcotics, is injurious because it may lower the irritability of the sensory nerves and thus diminish the cleansing effect of the expectoration which accompanies the cough, and may lead to a harmful accumulation of the secretion. This is true to a still greater degree, when, though the secretion is moderate, expectoration is deficient by reason of weakening of the expiratory muscles. Morphine is appropriate only when, the activity of the expelling forces being normal and the secretion scanty, there is a continued inclination to cough in consequence of hyperæsthesia of the sensory nerve terminations. This combination is often found in those suffering from phthisis; also in chronic bronchial catarrh, and in affections of the larynx. For asthma spasmodica see above. Morphine is of little *value in tussis convulsiva* (Stoll and others), and its employ-

ment in this disease is the more restricted because childhood itself is quite an important contra-indication.

Asthma bronchiale, in which narcotics and morphine above all are decidedly beneficial, should be also mentioned in this connection.

The best observers of former and recent times (Heberden, Laennec, and many others) have established that morphine can be employed only in the form called *asthma nervosum*, in which either no change or merely a pulmonary emphysema (secondary) can be physically demonstrated, and which is caused by spasm of the bronchial muscles. Morphine is also given in hæmoptysis, in which we consider it one of the best remedies.

It is true that it does not directly stop the flow of blood, and is ineffectual in very great, impeteous hemorrhages. When however, slight hemorrhage is kept up by continued inclination to cough, the employment of morphine becomes an imperative necessity, and its good effect is more striking than that of any so-called styptic.

The use of morphine in heart-disease demands special consideration. In organic affections of the heart it generally plays a subordinate *rôle*, and tried observers of great experience (as Laennec and many others) scarcely mention it in this connection. Digitalis is the morphine of such patients.

Morphine is even decidedly injurious when there is great engorgement in the venous system, or when cyanosis supervenes. It can only be employed to advantage when the patient is pale and anæmic from loss of sleep and oppression; when the blood is not overcharged with carbonic acid. This condition is caused, most frequently, by deficiency of the valves of the aorta. Even then only small doses should be given, and with caution. Yet all these considerations fail and morphine becomes indispensable in all forms of heart disease, when violent pain and oppression set in shortly before death.

Vomiting. — Morphine may, indeed, sometimes provoke vomiting. In many, even small doses have this effect. But such small doses generally lessen persistent nausea and check violent vomiting. For this reason morphine is much employed under the following circumstances: First, morphine is sometimes added to a drug which, when introduced alone into the stomach, may cause vomiting, as for instance, *chloride of mercury*. It is also used in the immoderate

vomiting which appears as a symptom of severe diseases of the stomach (ulcus, carcinoma) in vomiting from the abuse of alcohol and in the vomiting which, together with sleeplessness or disturbed sleep, affects those who have been reduced by the lack of their customary food, by overwork, or by other exhausting influences (Budd). Finally, it is used in so-called sympathetic vomiting, which occurs in many diseases of the various abdominal viscera, without an affection of the stomach proper.

Diarrhœa.—As opium, rather than morphine is almost always employed in all diseases of the intestines, accompanied by diarrhœa, we discuss them under the head of opium.

As counter-indications to morphine, or at least circumstances which allow its use only with the greatest precaution and circumspection, we mention the following: Firstly, childhood, especially during the first two or three years of life. It should be given during this period only in urgent necessity; also, in great reduction of the vital powers, especially when disease of the respiratory apparatus is present. Then, the condition called hyperæmia of the brain; additional circumstances, which restrict its use, have already been mentioned in the above description.

Dosage and Preparations.—1. Morphinum (ad 0.03 pro dosi! ad 0.1 pro die!) is little used in therapeutics, one of its salts being almost always employed.

2. Morphinum hydrochloricum, from 0.005 to 0.03 pro dosi (ad 0.03 pro dosi! ad 0.1 pro die!). For children 0.001 to 0.003, given in powders, pills, drops, and mixtures. The endermic method of administration, formerly employed, has now rightly been entirely superseded by hypodermic injection. The dose for injection must be the same as for internal application. Injections must be employed generally when exhibition *per os* is impossible, as in stricture of the œsophagus, violent vomiting, etc. Injection is also preferable when it is desired to produce the effect as quickly as possible, when a local action is required simultaneous with the general effect (in neuralgia for example); when strong gastric complication is present, and when, the prolonged use of the drug being necessary, it is desired to avoid disturbance of the appetite.

3. Morphinum aceticum
4. Morphinum sulphuricum } Given in the same doses as the above.
5. Trochisci morphini acetici, each containing 0.005 morph. acet.

OTHER ALKALOIDS OF OPIUM.

Narcotine, $C_{22}H_{23}NO_7$, crystallizes in brilliant prisms; it is tasteless, insoluble in water and alkalies, and soluble in alcohol and ether. *It is a mon-acid base,* the salts of which crystallize with difficulty, and *are of a very bitter taste.*

After morphine it ranks as the alkaloid which occurs in largest quantities in opium. Narcotine varies between four to six per cent. Fronmüller assumes that the amount of narcotine in opium bears a reverse relation to the amount of morphine; those classes of opium which contain much morphine contain less narcotine, and vice versa.

Physiological Action.—It appears that various observers have employed various preparations in their experiments, and that some of the specimens used contained adulterations of morphine. Almost all agree that small doses given to animals exercise a stupefying and hypnotic effect, followed by twitchings and convulsions, and finally produce death by general paralysis (Orfila, C. Bernard, Kauzmann). Most investigators coincide in the necessity of giving larger doses than if morphine were employed, to produce sleep and coma in man and animals, but the doses differ remarkably; thus, Schroff produced somnolency in his scholars after giving 0.15 grammes; Fronmüller observed sleep upon 1.0 to 1.5 grammes; the latter considers it among the most active of the alkaloids of opium aside from the necessity of giving larger doses. Ott does not consider narcotine an hypnotic, but only a convulsive. Narcotine is not generally employed therapeutically, and appears to be unnecessary.

Narceïne, $C_{23}H_{29}NO_9$, crystallizes in fine white needles, and is slowly soluble in water and cold alcohol. Its crystallizable salts are separated into base and acid by water.

Opium contains very little narceïne, at most 0.02 per cent.

Its *physiological action* is similar to that of morphine. Many investigators contradict this, believing that their experiments on animals could be employed to refute the observations made by others on man, but this is not applicable, as, like morphia, animals are less susceptible to it. Of how little moment such a comparison is can be seen when we recollect that Baxt did not produce sleep by a subcutaneous injection of 0.1 grammes of narceïne in rabbits, and Mitchell found it inactive in pigeons, because morphine also acts upon those animals only when given in enormous doses.

Large doses (0.1 to 0.3 grammes) to animals and men (0.03 grammes) of narceïne produce a deep sleep which, according to C. Bernard, lacks all manifestations of excitement, and is more quiet than in the use of any other alkaloid of opium. Men also bear as much as 0.2 grammes without suffering the nausea, vomiting, and prolonged stupor which morphine produces. Its influence on respiration, pulse, spasmodic and peristaltic motion, diarrhea, perspirations, kidneys, and bladder is similar in action to but less intense than that of morphine (Rabuteau, Eulenburg, and others).

We must not pass over the fact that Fronmüller attributes no practical importance to narceïne, and claims for it but a trace of narcotic action in doses of 1.0 gramme.

Some desultory therapeutic experiments have been made with narceïne, but it has not acquired extensive practical importance as yet.

Codeïne (methyl-morphine), $C_{18}H_{21}NO_3$, is homologous to morphine, and crystallizes anhydrously in ether in large octahedra, but, when containing one molecule of water, in rhombic prisms. It is easily soluble in spirit and water (80 parts). One hundred parts of opium contain almost 0.6 parts of codeïne.

The *physiological action* of codeïne is similar to that of morphine.

Its administration to amphibious animals produces primarily a marked *increase of reflex irritability* and tetanic convulsions; and finally a loss of

sensation and motion while the circulation is still maintained (Albers, Falck, Wachs).

Small doses given to warm-blooded animals produce a rather light sleep, with considerable reflex irritability; large, poisonous doses increase the irritability in dogs and rabbits to such an extent that finally alternate clonic and tonic convulsions supervene, followed by death, with symptoms of general paralysis (Crum Brown and Fraser, Falck).

0.1-gramme doses to men (Fronmüller) produce all of the morphine symptoms, and sleep followed in four hours by violent, long-continued trembling as in animals (Schroff and Heinrich).

The essential difference between morphine and codeïne lies in the influence which the latter exercises after suppressing the functions of the cerebrum; it produces increased reflex irritability of the medulla spinalis; if the administration of morphine be pushed, sleep becomes more profound, and the reflex irritability reduced, while the continued administration of codeïne causes the sleep to be interrupted by general trembling, and later on by violent convulsions. The hypnotic dose for dogs is 0.05 gramme, in adult men it is 0.1 gramme. Children are violently affected by codeïne. It is not employed therapeutically.

Among the other alkaloids of opium which do not appear in greater quantities than one per cent of the drug, *metamorphine*, *cryptopine*, *opianine*, and perhaps also *papaverine*, act similarly to morphine, narcotine and narceïne, while *hydrocotharnine*, *porphyroxine* and *laudanine* act similarly to codeïne, producing hypnosis and reflex symptoms.

Thebaïne, the spasmodic action of which, in man, is denied by Fronmüller, and of which at most only 0.3 per cent occurs in opium, and *laudanosine* (Falck, Jr.), act principally by exciting spasm of the extensors, which spasm is but little less intense than that produced by strychnine, and certainly is much more violent than the spasm produced by the codeïne group. This effect occurs in cold- and in warm-blooded animals. *Thebenine*, derived from thebaïne by heat and an excess of nitric acid, possesses the same empirical formula, but does not act on the spinal cord by increasing reflex action, but by decreasing it (F. Eckhard), and therefore may attain importance in medicine because of its more intense action than morphine and its freedom from its tendency to irritation, especially in sensitive persons (Kobert); always providing that Kobert's experiments on frogs are verified in warm-blooded animals and man.

Rhoeadine is said to exercise no physiological action whatever.

Apomorphine has nothing to do with opium, as it does not occur in it, but is artificially produced by treating morphine with acids; therefore we do not consider it here, but in its place with emetine.

OPIUM, POPPY-JUICE.

Opium (opium smyrnæum, laudanum, meconium), as has been observed, is obtained by making incisions into the unripe seed-capsules of the papaver somniferum, and is the milky sap which exudes from them. This mode of obtaining it entails a useless waste, because the opium alkaloids occur everywhere in the entire plant, and they are lost in this oriental way of obtaining them. It would be more serviceable and cheaper to produce the alkaloids of opium from the entire unripe plant.

According to the source, opiums are distinguished as those of Smyrna

and Turkey. Egypt and East India also produce some. It is frequently adulterated in the trade, but its importation will probably soon be rendered unnecessary because of the increased cultivation of the poppy in Germany—more so, as the opium obtained from the German poppy is better and richer in morphine than the best and purest oriental opium. The German opium contains as much as 20 per cent of morphine.

Oriental opium varies in appearance. It is imported in brown or black loaves of an ovoid shape, weighing one half kilo and enveloped in poppy and sorrel leaves and strewn with sorrel fruit. These loaves are hard externally, while within they are soft and pasty, and consist of gummy grains which are closely pressed together. These grains are the drops of poppy-juice which have exuded and dried. Opium has a strong stupefying smell and a disagreeable taste, and is only partly soluble in alcohol and water. It contains the before mentioned alkaloids and the ordinary vegetable constituents. The German Pharmacopœia requires powdered opium to contain at least ten per cent of morphine, and it is a matter of regret that physicians and pharmaceutists possess no methods of determining this easily. The precise quantitive determination cannot be found without a great loss of time, and not at all by simple examination. Therefore this requirement of the Pharmacopœia is not practical (Mohr).

PHYSIOLOGICAL ACTION.

Opium produces all of the acute and chronic symptoms that morphia does, therefore we refer to what has been said about it.

The similarity of action follows from the fact that the best opium contains as much as 20 per cent of morphine, and that most of the other alkaloids of opium have a similar intoxicating and stupefying effect as morphine has. The sum of the substances that are similar to morphine in opium can be estimated at about nine-tenths ($\frac{9}{10}$) of its entire mass, and the most active constituents at four-tenths ($\frac{4}{10}$) of the entire mass of opium. Opium does not act according to the amount of morphine it contains, but according to its morphine *plus* the action of the other stupefying alkaloids.

But as the principal other narcotic alkaloids of opium, especially the narcotine, have an equal effect qualitatively to that of morphia, but a much weaker one in intensity, the intensity of the effect of opium cannot be equalled by the effect of four tenths, but by three or only two tenths of morphia; or, in other words: estimates as well as rough experience prove that quality and intensity of the effect of any quantity of the best opium is equal to smaller doses of morphia by two thirds. The smallest fatal dose for an adult is 0.2 gm. of opium and 0.06 grm. of morphia; the therapeutic dose of opium and morphia found empirically, shows *similar* difference.

The quantity of convulsive alkaloids in opium, especially codeine (which also has narcotic effects) and thebaine (to which Fronmüller ascribes a partially narcotic effect, similar to papaverine in man) in quantities up to 0.35 grm. (in opposition to experiments with animals), is so small that their effect is hardly seen in poisonous and even fatal doses, much less in medicinal ones. If we estimate the contents of convulsive alkaloids in opium to be three per cent, which is however too much, there would be only 0.003 grm. in the maximum dose of 0.1 grm. extr. opii. allowed for the adult; these 0.003 grm. would not suffice to cause convulsions in human beings, not even if 0.003 grm. of pure thebaine, the alkaloid of opium, which is considered the most violent tetanic one, were given. To this must be added that 0.1 grm. extr. opii. contains about 0.03 grm. of substances equal in effect to morphia (see above); but in this dose morphia has a decidedly depressing and paralyzing influence on the reflex nerve centres of the spinal cord, so that even if the dose of 0.003 grm. of convulsive alkaloids produce convulsions, this effect would be more than compensated by the paralyzing effect of morphia and similar substances.

The similarity of the quality of the effect of morphia and opium is shown even by a critical review of the differences described by Schroff, which although adopted thus far by all physicians and used by them as fundamental bases for all therapeutical uses, are nevertheless untenable to-day.

Schroff asserts that, with 0.15 to 0.22 grm. of opium he produced narcosis with sopor, or at least narcosis verging on sopor, though it was of short duration and without bad after-affects, while morphia in a larger dose than could be contained in 0.20 grm. *i.e.* 0.07 produced sleep only, but never soporous narcosis. This is contradicted by our experience and that of others; whilst 0.2 grm. opium is admitted to be a dangerous dose, a relief from pain, sleep, and constipation are often produced; but sopor rarely if ever. In a similar way doses of morphia, by over one half smaller than those which Schroff employed, *i.e.* 0.03 grm. pro die, and then even in divided doses, sufficed, with people who were not accustomed to its use to produce the same effects as by opium, *i.e.* sleep; on the other hand, 0.06 grm. morphia is considered the minimum fatal dose for adults, and must *therefore produce* very deep sopor. Furthermore, Schroff *claims that opium* at first increases the temperature, whilst

morphia reduces it. We do not possess any statistical tables about measurements of temperature for these substances, but we often find it asserted that small doses of morphia increase the temperature and that middle and larger ones reduce it; thus we see that small doses of morphia have the same increasing effect as opium, whilst large doses of morphia and opium decrease the temperature.

It is equally wrong to assert that opium increases the pulse in its primary effect, whilst morphia decreases it; for we know that both morphia and opium increase pulsation at first, but later on diminish it. Thus the last assertion only remains to be discussed, viz.: that opium produces less derangements of the stomach and digestive organs; that eventually vomiting is easier; that morphia injures the stomach more, produces quicker nausea and vomiting, and that these bad effects last longer. This true observation is, however, not due to a diversity in the quality of its effect, but to the slower process of the effect of morphia; we and others have observed that the same quantity of morphia, if given at once, produces nausea and vomiting easily; if divided into smaller doses, however, and given in intervals of five minutes, it rarely ever produces such results.

Perhaps the effect of opium on the intestines is better, for the reason that its effective elements in conjunction with its resinous elements are absorbed more slowly and can therefore exercise a longer effect on the intestines; for that reason also the general effects of opium very likely are slower.

Schroff's error originates in the fact that he overlooked the possibility of great individual differences in regard to quantity, excitability, and paralysis each human being shows in the use of opium and morphia; and that he drew conclusions from far too small a number of observations.

As opium has thus the same effect as morphia qualitatively; as opium, furthermore, is very different in its effect according to the year of its growth, or according to its source; as this disadvantage is increased by possible adulterations so that its proportion of morphia may vary between five and twenty per cent; and finally as morphia is a safe, reliable, easily attainable and purely chemical substance: necessarily the absolute superfluity of opium becomes obvious, as does its absolute capabilities of being replaced by morphia, except perhaps, for reasons stated above, when its *local effect is* desired in intestinal diseases.

In view of the immense benefit which opium bestowed for centuries upon suffering mankind, the majority of physicians will not readily relinquish this favorite remedy. We will never forget the great obligation we owe it, but we will console ourselves with the knowledge that we possess in place of the mother plant her purer and more reliable daughter, morphia, who will continue to relieve and cure pains, sorrow, and sleeplessness more surely than her mother did.

Therapeutic use.—We have shown that morphia can fill almost all the indications for opium. It is true that some physicians prefer opium in certain cases, as in the treatment of psychopathies, delirium tremens, as also for intermittent fevers, in conjunction with quinine. But there are no valid reasons for this; it is due more to habit. It is, however, different in the treatment of diarrhea. Although it is true that morphia also constipates, opium in substance or in its preparations nevertheless produces this effect easier, and in doses which are not accompanied by any marked, great effect upon the sensorium, the cause of which is explained above. Thus we understand that up to this time opium has been used almost to the exclusion of morphia in diarrhœic conditions.

It is really one of our most reliable, perhaps all together the best remedy for these troubles, and has the great advantage over all other remedies that it cures coexistant colic. A disadvantage lies in the increase of anorexia. It should also be avoided in *acute* diarrhœa, as should all constipating remedies, when it is due to an indigestion. As one of the most important contra-indications generally, in every form of diarrhœa, we repeat in infancy, especially the first two or three years, although even then opium is sometimes indispensable, when the diarrhœa cannot be stopped by any other means. Of different diseases in which opium is employed for constipation we mention especially so called rheumatic-intestinal catarrh, which ensues in healthy individuals after colds or exposure to drenching rain, and which is often combined with severe colics. It is true that opium usually leaves slight constipation and in such cases diminishes the appetite, but it almost invaribly relieves diarrhœa and pain. In such cases we find it invariably better to give a strong dose (15 drops of tinctura thebaica) repeated, if necessary, in six to eight hours, than to give small consecutive doses, of *course always* with special regard to individual peculiarities. We find it equally valuable in diarrhœa due to the

introduction of caustic substances; as also in the more chronic catarrhs of the intestines with follicular ulcerations (then in connection with other remedies). Opium has always been extensively employed in the diarrhea of consumptives. In such cases it ought, however, be postponed as long as possible, if light diarrheas happen in an early stage of the disease, either as an incidental complication or as a symptom of intestinal disorder. Indigestion, such as is so easily produced by opium, ought to be avoided in such cases, and very often simple dietetic rules suffice for this purpose. If, however, exhaustive diarrheas appear in an advanced stage, as a symptom of a tuberculous ulceration or of amyloid degeneration of the intestines, then opium is necessary and indispensable. The result is transient in the most favorable cases, but at the same time it relieves the colics which usually accompany tuberculous ulcerations, and also relieves the increased sensitiveness of the abdomen. The use of opium in the diarrhea of typhoid fever has been discussed.

The use of opium in dysentery was always as energetically opposed as it had warm defenders; Sydenham is prominent among the latter and Heberden with the former.

Only a few of the better observers agree with Heberden, for instance Cullen, while the majority, especially of prominent German and English physicians, up to to-day consider the opiates among the most valuable remedies for dysentery.

According to prevailing experiences opium is very valuable in the sporadic form of dysentery. Of course these are cases which would very often recover under simple dietetic regimen; but certainly opium relieves the most troublesome symptoms, as tenesmus (especially if applied locally) and diarrhea, and frequently shortens the course of the disease. In the more serious epidemic forms of dysentery, opium is useless, but the majority of observers agree that in most cases it is indispensable, combined with other remedies, for the relief of pains and tenesmus and to procure sleep; certainly no other treatment produces better results. Of course we must never give opium in dysentery nor in other diarrheas of indigestion, until after the solid contents of the intestines have been evacuated. Then it is very valuable to give injections of opium when tenesmus does not prevent their administration.

In cholera nostras opium is the most valuable remedy

when combined with a suitable dietetic regimen. Not so universally proven and appreciated is its value in Asiatic cholera. Curing the precursory diarrhea it shows itself of real value in most cases, but in well-defined cholera asiatica it is often absolutely useless. Various observers assert even that it is injurious when there are real rice-water discharges; at all events it must be omitted as soon as reaction sets in. As however, so far all other remedies have appeared useless, opium will for the present retain its place as a good symptomatic remedy in the treatment of cholera.

As to the value of opiates in arresting the peristaltic motions of the intestines, which necessarily appears very often in cases of peritonitis, we have expressed our opinion. We also think that in all forms of hemorrhages of the intestines, as far as they do not originate in their lowest parts and can consequently be treated locally, opium is of better use than the introduction of the so-called styptics. Opium is of the utmost importance in the treatment of the acute ileus and is highly recommended therefore by a great many experienced physicians. The use of drastics in ileus is not so general as it was formerly, but neither is opium employed as yet as generally as it might be. Leichtenstern, according to our opinion, correctly says that opium is the more indicated, the more acute and serious the symptoms are from the beginning, and the more intense the colic pains become. It must be avoided absolutely in paralytic ileus, whilst when there are symptoms of the gradual development of ileus, another treatment should be employed.

Among those diseases in which opium has been tried purely experimentally, we select *diabetes mellitus* for special mention. Its therapeutic value in this complaint is very doubtful; sometimes it is considered useful only to quench thirst; at other times directly healing qualities are ascribed to it (of late Pavy and others observed a complete disappearance of sugar, and thus perfect recovery after the use of opium and morphia). The diaphoretic effect of opium is more spoken of than really proven.

External Use.—In painful affections opium is often used in fomentations, dressings, etc. When the skin is intact it is entirely useless, as opium never penetrates the epidermis. It is used more frequently to relieve the pains in chronic ulcers, in gonorrhœa, in conjunctivitis, etc. In such

cases an influence of the tincture of opium on pathological secretions is claimed. Opium is also applied in clysmata, in diarrhea when medication by the mouth is impossible, or when it is desired to avoid its effects on digestion. But then the effects of opium on the organism appear almost as easily and as severely as if applied internally.

Dosage and Preparations.—1. Opium pulveratum, internally, 0.005 to 0.1 pro dosi (0.15 pro dosi! 0.5 pro die!) in powders, pills, rarely in fluids, because it easily forms sediments. As an addition to clysmas in the same dose as internally; for eye powders (1.6 parts). Inhalation and smoking of opium are unsafe and dangerous.

2. Extractum opii, red-brown powder of bitter taste, soluble in water, which it makes turbid. It is often preferred to opium in substance on account of its more even effect and greater solubility. The forms of application, and the doses are the same as in opium pulveratum (ad 0.1 pro dosi! ad 0.4 pro die!).

3. Pulvis ipecacuanhæ opiatus, pulvis doveri, consists of eight parts of kalium sulf. pulv.; one part of rad. ipec. pulv.; one part op. pulv.; thus ten parts of the powder contain one part of opium. Experience justifies the preference of this mixture to other preparations of opium to arrest diarrhea, and also for diaphoretic purposes, in doses of 0.1 to 1.0, usually plain in a liquid vehicle.

4. Tinctura opii simplex, tinctura thebaica, tinctura meconii, is of a dark reddish-brown, and its specific gravity is 0.978 to 0.982. Ten parts contain the soluble elements of one part opium pulv. (=20 drops of the tincture which contain 0.1 opium). Internally, 5, 10 or 15 drops (ad 1.5 pro dosi! ad 5.0 pro die!) alone or in mixtures; the same quantites are employed in injections.

5. Tinctura opii crocata, laudanum, liquidum Sydenham, vinum opii aromaticum, consists of sixteen parts of opium, six parts of crocus, one part of caryophyllium, one part of cass. cinnam, in 152 parts of sherry wine. It is saffron-colored, specific gravity is 1.018 to 1.0227; ten parts contain the soluble parts of one part of opium (thus twenty drops of the tincture contain 0.1 opium). It is employed in the same doses and in the same way as is tinct. opii simplex (ad. 1.5 pro dosi! ad 5.0 pro die!).

6. Tincura opii benzoica, elixir paregoricum, consists of one part of opium, four parts acid benz. sublimat. and two parts each of camphor and ol. anis. in 192 parts spir. vini rectificatiss. Its color is yellowish-brown; 200 parts of the tincture contain one part opium; on account of the small amount of opium it contains the effect of opium is crowded out by those of the acid benz. and of camphor. It is used principally as an expectorant in chronic bronchial catarrhs, and in phthisis. Dose, 20 to 50 drops pure, or in a syrup and mixtures (5.0 : 100.0).

7. Aqua opii is a watery distillation of opium which carries the flavor of opium, but none of its active constituents.

8. Syrupus opiatus is a superfluous preparation; 1000 parts syrup contain one part extr. opii. Dose, 1 to 3 teaspoonfuls.

9. Electuarium theriacassen theriacale, theriaca, theriac, is a mixture of a number of substances, of which opium is one. This preparation, fortunately, is obsolete, and never used any more, but it has been recalled to a place in the Pharm. German and therefore will be described. Theriac *contains one* part opium pulv.; three parts vin. Hispan.; six parts rad.

angel, four of rad. serpent, two parts each of rad. valer., bulb. scillæ, rhiz. zedoar., cort. cinnam., cassiæ, one part each of fruct, cardam. min., myrrh, ferr. sulf. pur., seventy-two parts mel. depur.

10. Emplastrum opiatum, s. cephalicum; capital plaster, (Hauptpflaster) is just as superfluous as theriac, and was reinstated in the same way. It contains eight elemi, fifteen terebinth, five cera flava, eight oliban. pulv., four benzœ pulv., two op. pulv. 1 bals. Peruv.

11. Pilulæ odontalgicae, tooth pills are a mixture of 5.0 op. pulv., rad. bellad., rad. pyrethr. pulv.; 7.0 cera flava; 3.0 oil amygdal; fifteen drops ol. cajeput and oil caryophyll. The mass is divided into pills, each weighing 0.05. They are inserted into carious teeth. The employment of fructus capita, s. capsulæ, papaveris, cordia, poppy-heads in decoction for internal or external use, and in poultices, is absolutely superfluous and even unsafe because of the uncertain and very small amount of opium they contain. The same applies to the syrupus (capitum) papaveris, syrupus diacodis, soothing syrup, which has also been reintroduced into the Pharm. Germ., and which contains three parts fructus papav. and ceratoniæ, two parts rad. liquir, fifty parts aq. comm. twenty-five sacchar.

Treatment of Morphia and Opium-Poisoning.—Acute Poisoning.—When it is effected through the stomach the poison must of course be evacuated first, and this is important, even when many hours have elapsed, for experience has shown that these poisons, especially opium in substance, may be long retained in the stomach. The best means to that end is the stomach-pump; whenever it is not at hand, an emetic may be given. But vomiting may increase the collapse, which has to be well considered when the action of the heart is reduced (von Boeck). Emetics often disappoint whenever there is a reduction of nervous sensibility. For this condition mustard was formerly given as an emetic, which, however, is not a recommendable procedure. At the same time a solution of tannic acid or preparations that contain tannin should be administered as direct antidotes, but it should be remembered that morphic tannate is by no means insoluble. If the symptoms of absorption of morphia exist, they must be treated symptomatically. As long as the patient is not competely comatose but only drowsy, he must be continually moved about; douches of cold water are then as advisable as they are in complete coma; furthermore strong coffee without milk and sugar should be administered, as should subcutaneous injections of camphor. If there is great diminution of respiration principal attention should be given to artificial respiration. Venesection is a two-edged sword; formerly it was employed on account the cerebral hyperæmia that was presumed to exist. It is avoided now because the cerebral symptoms have very little, if anything, to do with the hyperæmia, and because venesection can remove but very little morphia from the body, whilst on the other hand the weakness of the action of the heart may thereby be materially increased. As to the possible benefit of transfusion, our knowledge is as yet too limited to give it weight. The assertion that *atropia* is a direct *physiological antidote* to morphia has of late attracted much attention and has led to much experimentation. In this connection we would add to our remarks in the introduction to the alkaloids that there is no kind of antagonism between atropine and morphia. If both poisons be given at the same time *almost* always the poisonous effects of both become evident, especially *dryness of the mouth* and throat, with nausea (Witkowsky). The fact *that the pupil after being* contracted by morphia is again dilated by atro-

pia is no proof of special antagonism, because both poisons act upon the muscles of the iris differently. Though Binz and Heubach claim a special antagonism in regard to blood pressure, and assert that the blood pressure after being diminished by morphia is immediately markedly increased by atropia, it is true only in as far as atropia always increases the blood pressure, whether given in morphia poisoning or in the normal condition, and also when the blood pressure is normal or depressed in morphia poisoning. Here also are the points whence they affect the blood pressure differ materially, and often there is not even an apparent antagonism in the symptoms. Most experimenters therefore were obliged to deny the antagonism between opium and atropia. The many casuistic deductions from results in private practice in favor of this antagonism are no proofs, because very often apparently desperate cases of poisoning by either of the two recover perfectly, even if the proper antidote (morphia versus atropia and vice-versa) were not given, and because those cases which end fatally are more rarely published. In one regard atropia is said to exert a favorably modifying influence upon morphia—*i.e.*, by reducing the probabilities of vomiting and of gastricism to a great extent. Witkowsky recommends the addition of $\frac{1}{25}$ of atropia to each part of morphia for this purpose.

Chronic Poisoning.—Chronic poisoning by opium (eating, smoking) is hardly ever observed in Germany. According to all experiences its treatment would be indentical with that of poisoning by subcutaneous injection of morphia which has recently come in vogue. Boeck claims that the only salvation for strong people lies in sudden discontinuance, while Levinstein and others do not limit it to any class of patients.

But as this is not without disadvantages, for even dangerous collapse may ensue, it were better to send such patients to hospitals or asylums where they can be constantly watched, and the ways in which such patients obtain their favorite drugs discovered and cut off. Other observers discountenance sudden deprivation and have recommended gradual reduction. We have seen good results from either treatment according to individual cases, each one of which must be treated on its individual merits.

It is self-evident that, as Erlenmayer says, no effort to deprive patients of morphium should be made when it is the only means of relief from incurable painful diseases, and where its substitution by chloral or alcohol in large quantities which might become even more dangerous.

APPENDIX.

DRUGS THAT ACT SIMILARLY TO OPIUM.

Indian Hemp, Herba Cannabis indicæ. The hemp which grows in Germany is botanically identical with the so-called Indian hemp (cannabis sativa s. indica) but it has almost no narcotic effect, whilst Indian hemp growing in the tropics has this quality to a high degree. The active constituent of Indian hemp is not yet absolutely known; some claim that it is an amorphous, brown, non-introgenized resin, cannabin, small doses of which (0.05, grm.) produce narcosis; others insist that when this resin is separated from its contents of ethereal oils, it may safely be given in ten-fold larger doses, and that this ethereal oil, *cannabine, is the active constituent.*

Physiological Effect.—The resin which exudes, the best kind of which is

called *momia*, and an impure kind, *churrus*, and also the blooming end-parts of the hemp-plant are collectively known under the name of *hashish*, which is a favorite narcotic in the tropics. In Africa from Morocco to the Cape of Good Hope, in Persia, India, Turkey nearly three hundred millions of people give themselves up to its pleasures. Some smoke (its smoke is very agreeable), and some take variously named preparations of the resin from blooming branches alone or in coffee. Real hashish is prepared by cooking the leaves and blossoms of the hemp with water, with the addition of some butter and inspissated to the consistence of the extract; then, to improve the taste, sugar and spices are added. In consequence of the existence of so many different preparations, their unequal contents of active principles, and also because the individual effect is so different, the opinions of the influence of Indian hemp diverge materially; but the majority concede that it surpasses all remedies thus far known which influence the brain, in its immediate effect on fancy and imagination (Schroff). The blooming ends act most strongly in the production of pleasant hallucinations, the vinous extract and the preparations mixed with sweets have a less exciting and more of a narcotic effect (Schroff). Hemp acts differently from opium; it intoxicates without modifying consciousness; the hallucinations created by it are of a more exhilarating nature and are combined with a desire to laugh and to exercise the muscular powers; it injures digestion less, does not constipate and increases the function of the skin (Schroff).

In the following considerations we will combine the observations of Schroff, Fronmüller and others, on the *acute* effects of this remarkable herb. 4.0 grm. of cannabis indica, taken in an infusion by a very excitable young man, speedily produced vivacity, inclination to move around; his eyes glittered; a feeling of warmth extended from the stomach to the chest and head, which soon became dull and heavy; then noises in the ears ensued, with diminution of hearing and numbness of the hands and feet. The pulse was reduced from 80 to 66 within 50 minutes after taking the drug, and soon again rose to 73. One hour and a half after the first, a second dose, double the quantity, was given (8.0 grm.), whereupon the pulse decreased, but soon rose in half an hour to 114 per minute. At the same time an attack of furor ensued which showed itself especially in a strong development of his muscular power; he laughed, sang, ran around, danced rapidly; then he was attacked with a strong desire to destroy everything, when three strong men could hardly restrain the formerly feeble man. During all this time his consciousness never suffered; he could answer all questions correctly; his sensibility was essentially impaired; he violently pounded his hands upon a table without feeling any pain therefrom.

Schroff himself describes the action of Egyptian hashish, of which he took 0.07 grm. in the evening. One hour later he suddenly felt a strong roaring, not only in his ears but in the entire head; then his whole body appeared to him to be surrounded by bright light and to be transparent. Increased self-confidence and self-consciousness sent him through a whole series of visions which appeared very important to him.

According to Wood the sense of time and space is entirely lost, so that, for instance, small spaces appear vast.

Fronmüller gave an uneducated person 15 0 grm. of a preparation of oriental hemp (called radjumelectuary), whereupon he was attacked by *such a violent dizziness* and ecstasy that he could hardly reach his bed, was *unable to raise himself* up afterwards, and yet could see and hear every-

thing around him and could talk intelligently. His imagination carried him to Heaven and to the water; sometimes he played with angels, then he sailed in a boat with pretty young girls, and he even imagined that he was flying. Heinrich observed a poisoning with some hashish received from the Orient under the name of *birmingi*, a dose of 0.7 grm. of which produced a very brief excitement; immediately thereafter long continued, marked depression of the circulation and extraordinary depression and fear of death.

Schroff observed after taking 0.5 to 1.0 grm. of the vinous extract of hemp a steady fall of the pulse, diminution of consciousness, headache, faintness, somnolent tendency, deep sleep without effect on the sensorium commune, and without evil after-effects.

These cases show the impossibility of presenting a scientific, clear picture of the effects of Indian hemp. Even if the experiments with similar preparations are compared, results vary widely; for the intoxicated behave differently according to their degree of education, proclivities, etc.; thus it may be that the Oriental people have voluptuous dreams, as is generally asserted; whilst western people who experimented with it all deny any such experience.

The same difference as in the effect on the brain was observed in its effect on other functions. The action of the heart was found to be excited by some (Schroff, Moreau), and depressed by others (Heinrich), still others found it unchanged (Fronmüller). The pupil is generally described as dilated; the secretion of urine is usually increased. The temperature was sometimes lower, sometimes higher, according to its exciting or narcotic effect.

Sleep is very often produced by Indian hemp, either after excitement or more or less duration, or very quickly from the very inception. Experiments made on animals confirm either the exciting or the narcotic effect, without contributing anything further to general knowledge.

The chronic habit of eating hemp not only after some time leads to disturbances of nutrition, but very often to marked mental disorders, and even to idiocy.

Therapeutic Use.—The results of the experiments thus far made do not allow a definite conclusion on the therapeutical value of hemp, and it will be the more difficult to obtain decided results, as we do not as yet possess any sure equable preparation. Furthermore, individual susceptibility to hemp appears to differ very much, and experiences are very scarce on account of the existence of other effective hypnotics. Cannabis indica has been employed in many affections, especially those of the nervous system. It has been used most of all as an hypnotic, especially by Fronmüller, who experimented on 1000 patients with it. The principal diseases in which it was employed were: Phthisis (387 cases), "inflammations" (104), surgical diseases (116); rheumatism (110), and others. His tables show that the complete hypnotic effect of cannabis indica appeared 530 times, partially 215 times; 255 times it was slight or not at all, and pretty evenly divided in the different diseases, last of all with rheumatism; 0.05 grm. of the vinous extract, which was usually employed, was found the smallest effective dose. In a few cases disagreeable incidents were observed immediately after taking it, as vomiting, dizziness, headache; often (about in 12 per cent) there was dizziness and headache the next morning. Increase of pulse and respiration was never observed, but often a slight falling of the temperature (0.5°). Fronmüller arrives at the conclusion that Cannabis ind. is a fairly safe hypnotic

in large doses, and that the sleep produced by it is very similar to natural sleep. It has the advantage over the opiates that it does not disturb the appetite, nor does it constipate, nor affect the circulation, and, therefore, it may be used in feverish conditions. He also noticed that it acts after morphia has been found useless, and that it can thus be applied in its place; it is especially effective in opium eaters (Christison). But morphia has the advantage, where it can be given at all, in its effect being surer and stronger.

After all Cannabis indica is far less important now than formerly, because of the power given us through hydrate of chloral.

Experience with other diseases in which Cannabis indica has been occasionally applied successfully, as tetanus, diseases of the mind, especially melancholia, as also in chorea, delirium tremens, etc., are very meagre and contradictory. The same applies to metrorrhagia (with or without disease of the womb). We may here mention the results of observations by Clouston with Cannabis indica in diseases of the mind, who obtained good effects of a combination of the tincture with potas. brom. 2 grm. of each (three times daily).

Externally Cannabis indica has been applied to relieve pains, but without appreciable results.

Dosage and Preparations.—1. Herba cannabis is hardly ever used, its preparations being employed almost exclusively.

2. *Extr. s. Resina Cannabis indica*, soluble in alcohol, but not in water; Fronmüller uses 0.2 to 0.5 grm. (the official maximum dose is 0.1 to 0.3 pro die) in pills or alcoholic extract.

2. *Tinctura Cannabis indica*, ex extracto, 5 to 20 drops (0.3 to 1.0) alone.

Poison-lettuce.—Two preparations of the poison-lettuce are made; they are:

1. *Extr. lact. virosæ*, a brown extract of the juice of the fresh plant; perfectly soluble in water.

2. *Juice of lactucarium* (germanicum), prepared from the inspissated juice of the lactuca virosa. It is obtained in irregular, yellowish brown, friable pieces, barely soluble in water, of a bitter taste and a strong, poppy-like smell.

From both of these a series of materials of varying purity are produced. They are lactucine, lactucapicrine, lactucon and lactucinic acid. Among these, crystalline, bitter *lactucine*, $C_{22}H_{13}O_7$, which is soluble in hot water and alcohol, has been found to be the efficient ingredient (Kromayer, Ludwig).

The lactucarium gallicum obtained from our lettuce, lactuca sativa, is no more officinal.

Physiological Effect on Man.—Crystalline lactucine, according to the experiments of Fromüller, does not always produce a specific effect in doses of 0.5 to 2.5 grm.; other narcotic manifestations, farther than constipation, have not been observed in its use.

Lactucarium Geramanicum has a stronger soporific effect than lactucine (Fronmüller). Its effect is very variable because of the very varying amount of active principles it contains. Besides sleep (Fronmüller) observed buzzing in the ears, giddiness, headache, torpor, enlargement of the pupil and frequently strong perspirations. Adults require 0.5 to 1.8 grm. to produce sleep.

Its Effect on Animals.—We shall cite only the very complete experiments of Skworzoff-Sokolowski on cold-blooded animals and mammalia,

in which he employed hypodermic or intravenous injections of poison-lettuce.

Voluntary and reflex motions and sensation of pain decrease more and more, and finally cease altogether. A true soporific effect on animals cannot be claimed; the final stupor and depression seem to depend not so much on a direct cerebral effect as on reduced circulation and respiration. The spinal cord is paralyzed finally from above downwards progressively. Equally the reduction of irritability of the motor nerves advances from the centre towards the periphery.

The striped muscles retain their irritability. Accelerated action of the heart is succeeded by a decrease thereof. The restraining apparatus of the heart is eventually paralyzed. Finally the blood-pressure sinks, partly on account of heart-weakness, partly on account of central vaso-motor paralysis.

Respiration likewise decreases after primary acceleration.

Death results from paralysis of the heart.

We would add to this that animals require enormous doses of morphine to produce sleep; hence the hypnosis of animals affords no criterion for men.

Therapeutically it is entirely superfluous. Inasmuch as the preparations of opium and chloral give us approved and safe hypnotics, there is no object in continuing the use of such a poorly proven preparation.

The officinal limit of the doses are: Extractum lactucæ virosæ ad 0.5 pro dosi! ad 2.5 pro die! and of lactucarium ad 0.3 pro dosi! ad 1.2 pro die!.

Hop-flour, Glandulæ Lupuli consists of the small resinous glandules of hop-blossoms or cones (strobili s. coni lupuli) obtained by sifting the latter. Hop-flour is also called *lupuline*, which may lead to the impression that it is a simple chemical element, which of course would be an error.

Hop-flour is a reddish-yellow, fine powder, which it is difficult to moisten with water, but which readily admits alcohol; under the microscope each single grain appears of a conical shape, of cellular structure, the interior of which is filled with an amorphous yellow resinous mass; the odor is aromatic, benumbing; its taste aromatic, bitter. It contains a terebinthine and oxyenous oil, on which its odor depends: *Hop-oil* and a crystalline bitter which is insoluble in water and soluble in alcohol, which is the bitter hop acid, and may be called *lupulite or lupuline.*

Physiological Action.—In small quantities hop-flour is gen-

erally credited with the production of a sensation of warmth in the stomach, increase of appetite, and augmented peristaltic motions.

In larger quantities the benumbing effect of hop-flour becomes prominent, so that even a lengthened presence in rooms or in places where hops are stored and where the air is saturated with the vapors of hop-oil produces numbness in the head, headache, even slight drowsiness, similar to air in which turpentine or other gaseous oils are suspended. Whether this headache is only a consequence perhaps of a reflex change of the cerebral circulation or a symptom of general poisoning is uncertain. Internally, hop-flour has not been observed to produce headache. Hop-flour seems to lack positive hypnotic properties.

Barbier found in numerous experiments on patients that hops neither produce sleep nor diminish irritability, and the digestion is not deranged; generally it does not attack the brain nor the spinal cord.

Fronmüller gave several healthy men 30.0 grms. of hop-flour in two parts within a few minutes, without producing a change of pulse, of respiration, or of temperature, nor of the size of the pupil, without even a trace of somnolence; once, brief transitory vertigo was observed; the appetite and digestion suffered no change. Nevertheless, the benumbing and soporific effects of beer are ascribed to the hops it contains.

The great contradictions and gross superficiality of the preceding matter render further investigations desirable.

Therapeutic Application.—Hop-flour is employed in dyspeptic conditions when the indications call for other aromatic bitter remedies, but as it is inferior to many of them its use can be dispensed with.

If it is desired to administer it, the best in form would be in beer well charged with hops, if the case will admit of this beverage.

Its use as a hypnotic and narcotic is perfectly superfluous, being far too unsafe and little approved. Of late, hop flour has been used much to reduce morbidly increased irritability of the sensitive nerves of the genital apparatus in its divers affections: in priapism and pollutions, especially in onanists; in chordæ veneræ resulting from gonorrhœa, in satyriasis and in nymphomania. There are a series of *reports which* assert that it proved beneficial in such cases. *Whether and* under what conditions it does more than

other remedies, especially opium and belladonna, cannot be told.

Dose: *Glandulæ lupuli:* 0.3 to 0.5 pro dosi (10.0 pro die) internally in powders, pills, alcoholic solution.

Gelsemium Sempervirens and Gelsiminine.—Gelseminine (Sonnenschein) is the active alkaloid of the root (rhizoma) of gelsemium sempervirens, a handsome American creeper. The salt, *gelsemininum muriaticum*, made by Schughardt in Görlitz, is a yellowish-white powder, consisting of fine crystals, which are easily soluble in alcohol and glycerine, less so in chloroform, and not at all in ether. In water it dissolves at 15° C. in a proportion of 1 : 40, and becomes neutral fluid, which foams pretty strongly when agitated and which becomes mouldy when undisturbed for a length of time, but remains clear when chloral hydrate or salycilic acid are added to it (Moritz).

Tromsdorff's gelseminine, formerly considered an alcohol, is at any rate impure; probably it is only a kind of extract.

Physiological Effect.—According to Burger, Ott and Moritz, the following are the principle effects both of gelsemium extracts and tinctures, as of gelsiminine:

In warm-blooded animals the first marked manifestation is a peculiar influence on the motor apparatus in the shape of paroxysmal tremblings of varying intensity of the head and of the superior, sometimes also the inferior extremities; and ataxia of the extremities, now resting upon their anterior aspect, then approaching the hinder legs almost unto overlapping; then making abnormal running motions. Thereupon a decrease of motility sets in, which, with a contemporaneous decrease of respiratory action, presents the symptoms predominant in later stages of poisoning. Decreased sensibility appears only when the prosoning is far advanced. Coincident with the decrease of respiration the heart's action becomes slow, and the temperature sinks considerably. Sometimes salivation supervenes, and when the poison is introduced into the conjunctival sac, unilateral mydriasis and paralysis of the accommodation sets in.

Death always occurs from respiratory paralysis.

In cold-blooded animals (frogs) similar phenomena are observed, only that the primary motor disturbances are less conspicuous, and the sensory spinal conductors are paralyzed, while the motor ones are in a state of abnormal irritability.

In men, some (Jurasz, Wikham, etc.) think that they have observed quick and sure removal of neuralgias by tincture of gelsemium, while others, especially Berger, decidedly deny it. The latter observed after giving the extract as well as the tincture only unpleasant symptoms, such as numbness in the head, giddiness, diplopia, impeded lingual motility, trembling of the hands, numbness of the fingers, nausea, vomiting, difficult breathing, general chilliness. The minimum deadly dose for rabbits weighing one kilo was found by Moritz to be 0.0005 to 0.0006 grm. From his experiments on animals it is calculated that the minimum fatal doses to men would be 0.03 to 0.06 of Sonnenschein's and 0.3 to 0.4 of Fromsdorff's gelseminine, the same (0.3) of the American fluid extract of gelsemine (Wormley), 36.0 of the tincture gelsemii e rad. rec., and 1.8 to 2.0 of both extracts.

Gelsemium is valued as a remedy for toothache without periostitis or gingivitis. Our personal experiences in neuralgias do not allow us to testify to any reliable effect of gelseminum.

(1) *Radix G. pulv.* is administered in 0.05 to 0.2 doses three times a day; strongest single dose is 0.25, and the strongest daily quantity 1.0.

(2) *Extr. G. fluidum* is given in 0.05 to 0.2 doses three times a day; the strongest single dose 0.25, and the greatest single dose per day is 0.75.

(3) *Tinctura gelsemii* is used internally and externally: internally, 0.5 to 1.0 every five hours in water; strongest single dose 2.0 (fifty drops), strongest daily single dose 6.0. Still the different preparations seem to be of different strength, wherefore Moritz recommends before applying an unknown preparation to first test it on rabbits.

Coto-barks, Cotoine and Paracotoine.—The coto-barks hail from Bolivia, look somewhat like quinine, and two kinds are known to commerce—viz., cortex verus and cortex para. Both have a resinous aromatic smell, the cortex verus a sharper one. In other properties the latter appears more indifferent, while the cortex verus has a sharp acrid taste. It increases the salivary secretion, and acts strongly irritating on ulcers, and often causes nausea and vomiting in man.

Their active principles are (1) those of the cortex *coto: cotoine* $C_{22}H_{18}O_6$ of a sharp balsamic odor, not easily soluble in cold water and readily soluble in hot water; (2)

those of the cortex para: paracotoine $C_{19}H_{12}O_6$, which is almost insoluble in water, only slightly soluble in potash and soda lye.

Both substances proved quite inactive in rabbits, even in doses of 1.0 grm. Healthy people who took single daily doses of from 0.05 to 0.1 grm. of paracotoine five to six times in succession noticed only slow peristaltic action or constipation, and no other symptoms, no inclination to vomit, nor any gastric complaints. It was excreted with the urine within four to six hours (Burkart).

In *therapeutics* paracotoine receives preference, as it is better born, and because it produces no irritation even to most susceptible stomachs in gastric catarrhs. The barks are not given any more. It has been especially recommended for acute and for chronic intestinal catarrhs in children and the diarrhœa of phthisis. In gastro-enteric catarrhs, which come on very suddenly with violent colics, opium emulsion will act more promptly and satisfactorily, while in subacute enteritis cotoine and paracotoine prove beneficial even when opium fails. Cotoine is given in 0.05 to 0.1 grm. doses daily; paracotoine 0.1 to 0.2 every two or three hours. Because of the difficulty of dissolving them they are given in powder, with sugar.

Aspidosperma Quebracho and Aspidospermine.—The bark of aspidosperma quebracho (according to Fraude, probably identical with Leopterigium Lorentii Griesebach) a native tree of the province of Santiago, of the family of the apocyniæ, is used in its native place as a febrifuge. The wood thereof is imported by us for tanner's material. Baeyer prepared an alkaloid from the bark. Aspidospermine $C_{22}H_{28}N_2O_2$, which is easily soluble in alcohol and ether, very little in water. Its taste is bitter. The extract prepared by Penzoldt from the cortex Q. and the above-mentioned alkaloid have a similar effect on the frog. The lignum quebracho, which contains very much tannin, also seems to contain aspidospermine, though in much smaller quantity; hence its effect, although similar, is much weaker.

Physiological Effects.—Penzoldt's experiments with an extr. cort. quebracho yielded the following results:

In frogs 0.5 of the bark produced complete motor paralysis of central origin to the degree of contemporaneous paralysis of respiration and of the extremities. The pulsations of the heart were reduced by one half in

consequence of weakened motor elements. Reflex irritability lasted somewhat longer than did voluntary muscular movements.

In rabbits small subcutaneous doses (corresponding to 1.0 grm. of the bark) produced paralysis of the extremities and impeded respiration, and large doses (2.5) caused death after producing paralysis of voluntary motions, great dyspnœa and convulsions. Respiration appeared deep and retarded; the pulse and blood-pressure, however, sank only after direct injection into a vein.

Its action when applied to dogs was similar, except that the dyspnœa was combined with an increased number of respirations; salivation set in besides. The normal as well as the fever temperature (in artificial putrid fever in dogs) likewise in feverish people was rarely disturbed. Penzoldt also found only that it delayed the decomposition of proteine substances without completely arresting it.

Therapeutic Application.—The quebracho bark was recently recommended by Penzoldt as a remedy, the effects of which are free from disagreeable concomitants, temporarily diminishing or removing various forms of dyspnœa in diseases of the circulatory and respiratory apparatus (mostly in emphysema; its action is less certain in phthisis, and quite uncertain in nephritis when œdema is present). This effect is manifested in decreased frequency and depth of the respirations, decrease of cyanosis, and, above all, of the subjective symptoms. Since Penzoldt published these observations last year they have been substantially confirmed more or less extensively. Some observers could obtain no convincing results, and our personal experiences (Nothnagel) mostly resulted at least negatively. These failures, however, do not warrant a denial of its action, especially as the drugs ordinarily obtained seem to vary materially, and the trials were by no means all made with the bark, but often with the less active wood, and with a still weaker extract of the Q. A. Judgment should be suspended until numerous experiments have been made with the same preparation, or, better yet, with the alkaloid.

The experiments made certainly invite to their continuance, as the results obtained promise a specific in dyspnœa, when produced by overcharge of carbonic acid gas or lack of oxygen. Penzoldt also draws attention to the fact that

at all events the efficient doses should at first be carefully elicited.

Dosage.—Cortex (lignum) Q. subtilissime pulv. 10.0 macera per dies vii, in vitro bene clauso cum spir. vin. rectificatiss. 100.0, dein filtra et inspiss. solve in aq. fervid. 20. Filtra. D. S.—1 to 2 teaspoonsful once to thrice daily.

APOMORPHINE, EMETINE, AND COLCHICINE.

The remedies comprised in this group (emetine, apomorphine, and tartar emetic) are generally classed together as "Emetics." This is, however, not any more practical on account of their exercising a marked effect on the central nervous system, the heart, and partly paralyzing the muscles of the Rana temporaria (Podwyssotzki), likewise on the striped muscles of the body.

An unmistakable limited analogy exists between apomorphine and morphine (Harnack). The physiological effects of both differ from each other only in degree. Apomorphine, like morphine, primarily produces excitement, vomiting, accelerated breathing, only that the excitement produced by the former manifests themselves stronger, clearer, and more certain. Finally, morphine as well as apomorphine paralyzes the central organs; only the former does it more quickly and with smaller doses.

Colchicine ranks next to emetine in physiological effects. The tartrate of antimony and potash (which has been discussed) exercises the same general influences upon the skin, nervous system, stomach, etc., but with somewhat more severe topical effects than emetine.

Violine, the alkaloid of the fragrant violet (viola odorata), is said to produce effects resembling those of emetine and apomorphine, as do cyclamine (from the tubers of the cyclamen europæum), and the asclepiadine from the roots of Vincetoxicum officinale.

APOMORPHINE.

Apomorphine, $C_{17}H_{17}NO_2$, is readily soluble in alcohol and ether. It is a white powder which results from heating morphine with concentrated muriatic acid to 150°, by which a molecule of its water is driven off. In the atmosphere and in aqueous solution it soon assumes a green color, *without essential* loss, however, in its characteristic effects

PHYSIOLOGICAL EFFECT.

Animals who readily vomit (as the dog, the cat, man) after taking small quantities of apomorphine manifest no specially marked symptoms but emesis. Very small, non-emetic doses are said to facilitate expectoration, as do the other emetics.

When given internally and subcutaneously to man 0.005 to 0.01 grm. of apomorphine are required to produce nausea and vomiting in 5 to 20 minutes. The emesis produced is similar to but milder than that caused by tartar emetic and ipecacuanha. These symptoms, which are accompanied by increase of the number of respirations and pulsations, render a detailed description of the symptoms and causes unnecessary here, as they were discussed under tartar emetic. The violent collapse, however, which the latter produces is seen in the use of apomorphine when given to little children. The smallest non-emetic doses generally produce longer nausea than do doses which excite vomiting. Within a few minutes after vomiting marked sensations of comfort may return; sometimes also fatigue and sleep supervene (See, Pierce Siebert and others). Very large doses (0.2 grm.) evidently paralyze the same apparatus, the excitement of which by smaller doses produces vomiting. Thus dogs vomit readily after small doses, but cannot after taking large ones. Instead, however, stupor, loss of reflex irritability, and paralysis of the hind feet occur in them (H. Köhler and Quehl). Siebert, after giving 0.06 to 0.1 grm. to cats and dogs, observed great fear, gyratory and leaping motions, enlargement of the pupil and salivation. Doubtlessly similar appearances would set in also in men; but, as far as we know, no such large doses have yet been applied to them.

In those animals whose organization renders vomiting impossible, as for instance in rabbits, the excitement and paralysis are particularly prominent, hence we deduce that numerous centres of the brain and of the medulla oblongata, especially those of the motor, partly also those of the sensory sphere, appear to be affected, for we have unwonted *dread, incessant* motions, chewing, gnawing, very severe *acceleration* of respiration, finally convulsions, paralytic *manifestations*, and death with dyspnœa (Harnack).

Consequently apomorphine acts on individual organs and functions as follows :

Brain and Spinal Cord.—The central organs of sensation are excited in frogs, rabbits, and cats. This has not been confirmed in dogs or guinea-pigs. The centres of voluntary motion are highly excited in frogs and rabbits, and are subsequently paralyzed in frogs, probably would also be in man and dogs. The respiratory centre is severely excited in rabbits and dogs, finally paralyzed in the former, but not in dogs, even after doses of 0.6 grm. The centre for vomiting is excited by small doses, and probably paralyzed by large ones.

The peripheral nerves of both orders are not paralyzed. The heart's nerves of acceleration are excited, hence the quickening of pulse while the pressure of blood remains unchanged.

The striped muscles of the body and the cardiac muscle are paralyzed in the frog with certainty, but they do not become rigid; in mammalia and man this is not yet ascertained.

The temperature sinks gradually.

THERAPEUTIC APPLICATION.

Apomorphine is chiefly applied as an emetic when it is indicated. Its advantages over tartar emetic, ipecacuanha, sulphate of zinc and copper are the following: Firstly, it is reliable; next, it permits of the possibility of subcutaneous injections, which act in very small doses, and no abscesses result in the places where injections are made; such possibility of subcutaneous introduction as need not be detailed is quite of essential import in comatose conditions, in mental alienation, etc. Another agreeable circumstance is this, that the prodromal manifestations are very brief and very insignificant when pure preparations are employed. The quantities hitherto applied are almost entirely bereft of all disturbing, noxious, or dangerous after-effects and concomitants, which is an important consideration in its favor.

Apomorphine is, moreover, recommended as an expectorant in bronchial catarrh (Jurasz), when conditions prevail like those that call for ipecacuanha. This effect has been confirmed by some observers; however, it has thus far not been extensively employed in practice.

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Violine, the alkaloid of the fragrant violet (viola odorata), is said to produce effects resembling those of emetine and apomorphine, as do cyclamine (from the tubers of the cyclamen europæum), and the asclepiadine from the roots of Vincetoxicum officinale.

APOMORPHINE.

Apomorphine, $C_{17}H_{17}NO_2$, is readily soluble in alcohol and ether. It is a white powder which results from heating morphine with concentrated muriatic acid to 150°, by which a molecule of its water is driven off. In the atmosphere and in aqueous solution it soon assumes a green color, without essential loss, however, in its characteristic effects

PHYSIOLOGICAL EFFECT.

Animals who readily vomit (as the dog, the cat, man) after taking small quantities of apomorphine manifest no specially marked symptoms but emesis. Very small, non-emetic doses are said to facilitate expectoration, as do the other emetics.

When given internally and subcutaneously to man 0.005 to 0.01 grm. of apomorphine are required to produce nausea and vomiting in 5 to 20 minutes. The emesis produced is similar to but milder than that caused by tartar emetic and ipecacuanha. These symptoms, which are accompanied by increase of the number of respirations and pulsations, render a detailed description of the symptoms and causes unnecessary here, as they were discussed under tartar emetic. The violent collapse, however, which the latter produces is seen in the use of apomorphine when given to little children. The smallest non-emetic doses generally produce longer nausea than do doses which excite vomiting. Within a few minutes after vomiting marked sensations of comfort may return; sometimes also fatigue and sleep supervene (See, Pierce Siebert and others). Very large doses (0.2 grm.) evidently paralyze the same apparatus, the excitement of which by smaller doses produces vomiting. Thus dogs vomit readily after small doses, but cannot after taking large ones. Instead, however, stupor, loss of reflex irritability, and paralysis of the hind feet occur in them (H. Köhler and Quehl). Siebert, after giving 0.06 to 0.1 grm. to cats and dogs, observed great fear, gyratory and leaping motions, enlargement of the pupil and salivation. Doubtlessly similar appearances would set in also in men; but, as far as we know, no such large doses have yet been applied to them.

In those animals whose organization renders vomiting impossible, as for instance in rabbits, the excitement and paralysis are particularly prominent, hence we deduce that numerous centres of the brain and of the medulla oblongata, especially those of the motor, partly also those of the sensory sphere, appear to be affected, for we have unwonted dread, incessant motions, chewing, gnawing, very severe *acceleration of* respiration, finally convulsions, paralytic *manifestations,* and death with dyspnœa (Harnack).

Consequently apomorphine acts on individual organs and functions as follows :

Brain and Spinal Cord.—The central organs of sensation are excited in frogs, rabbits, and cats. This has not been confirmed in dogs or guinea-pigs. The centres of voluntary motion are highly excited in frogs and rabbits, and are subsequently paralyzed in frogs, probably would also be in man and dogs. The respiratory centre is severely excited in rabbits and dogs, finally paralyzed in the former, but not in dogs, even after doses of 0.6 grm. The centre for vomiting is excited by small doses, and probably paralyzed by large ones.

The peripheral nerves of both orders are not paralyzed. The heart's nerves of acceleration are excited, hence the quickening of pulse while the pressure of blood remains unchanged.

The striped muscles of the body and the cardiac muscle are paralyzed in the frog with certainty, but they do not become rigid; in mammalia and man this is not yet ascertained.

The temperature sinks gradually.

THERAPEUTIC APPLICATION.

Apomorphine is chiefly applied as an emetic when it is indicated. Its advantages over tartar emetic, ipecacuanha, sulphate of zinc and copper are the following: Firstly, it is reliable; next, it permits of the possibility of subcutaneous injections, which act in very small doses, and no abscesses result in the places where injections are made; such possibility of subcutaneous introduction as need not be detailed is quite of essential import in comatose conditions, in mental alienation, etc. Another agreeable circumstance is this, that the prodromal manifestations are very brief and very insignificant when pure preparations are employed. The quantities hitherto applied are almost entirely bereft of all disturbing, noxious, or dangerous after-effects and concomitants, which is an important consideration in its favor.

Apomorphine is, moreover, recommended as an expectorant in bronchial catarrh (Jurasz), when conditions prevail like those that call for ipecacuanha. This effect has been confirmed by some observers; however, it has thus far not been extensively employed in practice.

Dosage.—Apomorphinum hydrochloricum, 0.002 to 0.005 to children, and up to 0.005 to 0.01 to adults, hypodermically, in aqueous solution, as an emetic; in adults only 0.1 to 0.18, in enema, and 0.1 to 0.2 for the emetic effect. As an expectorant the solution is given internally as high as 0.01 to 0.03 pro dosi. Blaser states that the instability of apomorphine solutions may be obviated by a solution of the muriatized preparation in syrupus simplex, which remains unchanged for weeks if kept in air-tight vessels.

EMETINE.

Pure emetine, $C_{30}H_{30}NO_5$, is a white, crystallizable, bitter, odorless alkaloid. It soon loses its white color and becomes yellow. In cold water it is but slightly soluble (1 : 1000), but it readily dissolves in alcohol, fat oils, etc. It is of an alkaline reaction, and is neutralized by acids forming salts with them, which easily dissolve in water, spirits, and fatty oils.

Genuine *radix ipecacuanhæ* contains from three fourths per cent to one per cent, the poorest sorts only from one fourth to one half per cent of emetine. Impure emetine (emetinum coloratum) is merely an extract of ipecacuanha and not a pure substance.

PHYSIOLOGICAL ACTION.

Pure emetine, the emetic principle of ipecacuanha is a very poisonous substance (rabbits and cats are killed by 0.025 grm., dogs by from 0.1 to 0.3 grm). Its physical action greatly resembles that of tartar emetic.

Local Effects.—Rubbed upon the skin, it produces dermatitis and pustules, which heal without leaving scars. Prolonged application of large quantities ulcerates the corium, in which case scars are, of course, formed. It produces violent stimulation and inflammation when applied to any mucous membrane.

Both in animals and men, doses of from 0.005 to 0.1 gramme cause a bitter, acrid taste and salivation. The same doses, whether given internally or in hypodermic injection, produce intense nausea, violent vomiting and diarrhœa.

The following are the results of the careful experiments made on animals by Schroff, Schuchhardt, Dyce-Duckworth and Podwyssotzki:

Emesis is by no means a positive and invariable result of emetine when given to animals that can vomit. In cats, for example, even relatively large doses frequently produce no emesis, especially when the poison is injected directly into a vein. Ordinarily, vomiting occurs within an hour after the drug has been taken, following no more

speedily upon internal application than upon hypodermic use. The vomiting is probably a reflex result of stimulation of the nerves of the stomach. The intestinal affection sometimes fails if vomiting occurs, as the latter immediately removes the poison.

In certain animals, however, diarrhœic discharges occur, even when vomiting takes place. The peculiarly characteristic evacuations of the bowels do not occur, according to Podwyssotzki, until after the expiration of 18 or 24 hours. These discharges are often mixed with blood and mucus.

The mucous membrane of the small intestine, and, to a lesser extent, that of the large intestine, sometimes shows only slight maculation and catarrhal swelling, but occasionally it is colored dark-scarlet throughout its whole extent and covered with a loosely-adhering purulent mucous secretion.

In the small intestine of the dog, sharply defined, round ulcers also occur in spots. Much detached epithelium and pus are always found in the contents of the intestine.

Several observers have clearly noticed, as an effect of emetine, a morbid condition of the bronchiæ and lungs, consisting in intense redness of the bronchiæ (Schuchhardt) and great hyperæmia, œdema and condensation of the stroma of the lungs (Duckworth, Podwyssotzki).

The manner in which these changes are brought about is still quite uncertain. They do not take place with certainty in all animals (Schroff).

General Symptoms.—During the period of nausea and vomiting, in men and animals, the frequency of the pulse and respiration is first increased, then diminished (Ackermann), and the temperature falls. Profuse perspiration also frequently occurs.

Effect on the Central Nervous System.—In man there is the aversion to bodily and mental labor usually incidental to nausea. Frogs, in from one half to one and one half hours after the injection of 0.005 to 0.1 gramme of emetine, fall into general paralysis, resulting from increasing paralysis of the central nervous system, without previous symptoms of stimulation. They also exhibit fibrillary contractions or the motion of vomiting so that the symptoms are quite unique. The irritability of the muscles is unchanged, at least in the rana temporaria. The heart soon beats irregularly, with increasing weakness, and finally stops, paralyzed in diastole. Mammals also evince great weakness and caducity in connection with marked reduc-

tion of blood-pressure, though the action of the heart remains strong and regular.

After small doses, the blood-pressure soon regains its normal value. The investigations thus far made do not enable us to trace all the above symptoms to their causes.

After fatal doses (see above) there is great muscular weakness, and death occurs in collapse. Cats fall down and die, amid very slight contractions, resulting from paralysis of the heart.

IPECAC, RADIX IPECACUANHÆ.

Ipecac, radix ipecacuanhæ, from *cephælis ipecacuanha* (Rubiaceæ), contains, in addition to the emetine above described, a tannic glycoside called ipecacuanic acid, starch and other bodies of no physiological importance.

PHYSIOLOGICAL ACTION.

The physiological action of ipecac is almost identical with that of emetine, though, of course, much less intense, so that only the following additional remarks are necessary. Very small doses of ipecac (0.01 gramme) are said to increase the appetite, but in many cases these cause nausea, especially when these doses are frequently given.

As an emetic, the necessary dose varies greatly with the varying richness in emetine. The emetic dose of radix ipecacuanhæ varies, therefore, from 0.1 to 1.0 gramme.

Ipecac, unlike emetine, is not followed by diarrhæa.

Powdered ipecac, mixed with bile, and introduced immediately into the duodenum of the dog, produces a stronger injection of the mucus membrane and increased secretion of mucus, and especially of bile, in the duodenum, without any cathartic effect (Rutherford).

Inhalation of the dust of ipecac causes violent sneezing and coughing, and sometimes dyspnœa.

THERAPEUTIC EMPLOYMENT OF EMETINE AND OF RADIX IPECACUANHÆ.

As yet emetine has not been generally introduced into practice, because the old custom of giving ipecac itself has been retained. We cannot say, therefore, whether the alkaloid should be used except as an emetic.

Husemann states that, in addition to the vomiting, emetine is much more apt to cause diarrheal discharges *than the root.* As the alkaloid can now be obtained in

pure condition (Podwyssotzki), it is much to be desired that it should entirely replace the root which so greatly varies in its proportion of emetine, and, therefore, in its effect. Ipecac in large doses, frequently, in combination with tartar emetic in the case of adults, alone in the case of children, is one of the most popular emetics at present. Its effect is certain. We cannot, of course, treat here all the indications of emetics in general.

These indications, indeed, have become greatly reduced in number in recent therapeutics. We merely mention the peculiarities which characterize the emetic action of ipecac.

The spasmodic efforts which precede vomiting are moderate; vomiting occurs only once or a few times, the collapse following each act is slight, and simultaneous effect on the intestines (diarrhœa) is exceptional. Ipecac therefore may be safely given to children and aged or weak patients. Ipecac is often used in small doses in the following cases. It is one of the remedies most used in *bronchial catarrh.* Since however it sometimes fails in practice, we are free to state that ipecac meets only symptomatic indications in bronchitis; that is to say, it probably causes coughing and hence promotes expectoration, but the course of the anatomical changes in the bronchial mucous membrane is not affected, and ipecac does not satisfy the *indicatio morbi.* We must also mention that, after very great experience with this drug, we question its utility in bronchial catarrhs. We will not make the statement that it does absolutely no good, but we have never found certain proof that bronchitis passes away more quickly or gives less trouble when ipecac is given than when it is not. The special conditions in which ipecac is customarily employed in bronchitis are the following: It is given when the catarrh is idiopathic and acute, when fever is present, when expectoration of thick secretion is absent or slight; also in so-called *catarrhus suffocativus*, when the acute form develops from long-standing chronic catarrh (with or without *volumen pulmonum auctum*), and is accompanied by violent dyspnœa, cyanosis, and fever. It is also given in the second stage of acute and in subacute catarrh, when the discharge is tough and scanty. Ipecac may always be given under the circumstances mentioned in secondary catarrh, even in patients suffering with phthisis. Given in so-called Asthma spasmodicum it affects merely the accompanying catarrh, as Laennec has remarked.

Ipecac is frequently given in *chronic intestinal catarrh*, ac-

companied by tenesmus and colic, if the appetite is good. It is generally used in connection with opium for this purpose. It has also been given with advantage in acute so-called *rheumatic intestinal catarrh* (diarrhœa following cold). Here also it is usually combined with opium (Dover's powders). The diminished efficiency with children is probably due to the omission of opium in their case.

The employment of ipecac in *dyspepsia*, though recommended by various observers, is of doubtful advantage. Indeed its prolonged use generally injures the appetite.

The views taken of the action of ipecac in *dysentery* (radix antidysenterica) have suffered frequent changes. While the majority of observers ascribe to it a favorable effect only in the later stage of light cases (here also used partly in connection with opium), it has in recent times been most strongly recommended by various physicians, both for the acute and the chronic forms of the disease. Some give it in large doses (1.0 to 1.5) in a bolus at intervals of from 12 to 24 hours. Possible vomiting should be prevented by laudanum, and sinapisms on the epigastrium. Others give it in infusion in small or moderate doses. Wernich considers ipecac as especially valuable in dysentery when a somewhat atonic condition if the intestine is fairly assumable.

The utility of ipecac in internal hemorrhage, convulsions and other "spasmodic" attacks and as a diaphoretic is very slight or entirely doubtful.

Dosage and Preparations.—1. *Emetine* is given as an emetic in powders or solution in doses of 0.005 to 0.02. Hypodermic applications are not made.

2. *Radix ipecacuanhæ*, as an emetic, 0.3 to 1.5 every 10 or 15 minutes, usually given in the form of powder with tartar emetic. (Ipecac 1.0, Tart. emet. 0.05). To children from 1.0 to 2.0 of ipecac should be given divided into two doses. It is also given suspended in a mixture. In *refracta dosi* from 0.01 to 0.05 pro dosi (usually 0.5 : 150.0) in infusion, mixture, powders or pills.

3. *Pulvis ipecacuanhæ opiatus*, see *Opium*.

4. *Tinctura ipecacuanhæ*, yellowish-brown, generally given in small doses of from 10 to 30 drops. As an addition to mixtures 5.0 to 6.0 : 150.0.

5. *Syrupus ipecacuanhæ*, light brown, given as an addition to other medicaments. Dose, a teaspoonful.

6. *Vinum ipecacuahæ* (obtained by macerating 1 part of the root in 10 parts of sherry wine), given in doses of from 10 to 30 drops.

7. *Trochisi ipecacuanhæ*, each weighing 1 grm. and containing those ingredients of 0.005 of the root that are soluble in hot water.

Tannin and medicines containing tannic acid are recommended as *antidotes in hyperæmesis.*

COLCHICINE.

In *Meadow saffron, colchicine autumnale* (colchicaceæ), especially the seeds, the chief active principle is *colchicine*, $C_{17}H_{19}NO_6$. Colchicine is a yellowish white, amorphous, bitter alkaloid readily soluble in water and alcohol. According to our (Rossbach and Wehmer) investigations, it is a poison which acts very slowly, and which is fatal to all animals and men in comparatively small doses. The true carnivora are the most sensitive (the minimum fatal dose for a cat weighing 3 kilograms is 0.005 grm.).

Herbivorous and omniverous animals are less readily affected (a rabbit is killed by 0.03 grm.; a man by 0.03 grm.). Cold-blooded animals are the least affected (frogs require 0.2 grm. to cause death).

When much larger doses are given the symptoms are not more evident, nor is death more speedy. The central nervous system is paralyzed after initial stimulation.

Very strong stimulation of the spinal functions in frogs is shown by tetanic spasms. Symptoms of stimulation are wanting, on the contrary, in men and all warm-blooded animals. The final paralysis of the central nervous system is equally complete in all classes of animals (and loss of consciousness and of sensation, disappearance of voluntary and reflex motions, reduction of, and finally paralysis of respiration). The peripheral ends of the sensory nerves are likewise paralyzed; the motor nerves and striped muscles, on the contrary, remain intact. The circulation is, in general, little affected either in warm or cold-blooded animals. The heart beats with unaltered force long after the death of the other organs, and almost up to the death of the animal. The death of the heart seems due not to colchicine, but to secondary changes in the blood (carbonic acid). The blood pressure long remains normal, not falling until shortly before death. The abdominal organs are affected with especial intensity, in particular the gastro-enteric mucous membrane in warm-blooded animals is enormously swollen, and becomes blood-red by injection, so that hemorrhages even take place in the intestinal lumen, and fearful colics, violent vomiting and diarrhœa occur. The abdominal branch of the vagus and the splanchic nerve are not paralyzed during the greater part of the duration of poisoning. Excretion of urine is always diminished (kidneys hyperæmic). Death is caused by paralysis of respiration.

Therapeutic Application.—Colchicine is employed in but a few circumstances, and its use is purely empirical. It was introduced in gout and rheumatism by Home, Copland, and Williams in the first quarter of the present century, and has since been a favorite remedy in gout. Our own experience with gout being insufficient, we quote English physicians. Its mode of action in gout is still uncertain. The hypotheses built upon increased excretion of uric acid have no physiological foundation.

Still, to particularize, it is of decided benefit (according to Todd, Garrod, and others) when the patient is young and robust, when the gout is not of too long standing, and in acute attacks. It must be employed with caution if the patient is old or weak, and should be used in chronic gout only in acute exacerbations. The beneficial effect of colchicine is produced in the cases specified without the induction of vomiting or diarrhœa. On the contrary, if evacuation of the bowels is indicated it must be effected by a saline aperient. Some physicians commence with a full dose, 2.0 to 4.0 vin. sem. C., and follow with smaller doses; others begin with quite small doses, and gradually increase them. It has occasionally proven efficacious in attacks of so-called irregular gout (gout

in the head, etc.) as well as in gout proper. Still colchicine is not a remedy for the morbid process, which is the basis of gout, but is only of benefit in individual paroxysms. The value of colchicine in *rheumatism* is more than doubtful. Some observers claim to have found it useful in acute articular and muscular rheumatism, others in chronic rheumatism. Some of the latter value it especially when it produces alvine evacuation, others when it does not. At all events it is evident from the observations that have been made (Eisemann, Skoda, Andral, Monneret and others) that colchicine has no decidedly favorable effect in any particular form of rheumatism.

It is in fact difficult to arrive at a certain conclusion from the empirical results, when such an observer as Andral, for instance, considers the medicine entirely uncertain, while Skoda, on the contrary, praises it.

We know nothing of the subject from our own observations. Heyfelder has recently recommended hypodermic injections of colchicine in chronic rheumatism of the articulations and rheumatic neuralgia; 0.001 to 0.002 should be injected in the vicinity of the parts affected.

Further experiments on this point are desirable. Rossbach, from the results of his investigations, finds no indication for the useful application of colchicine, except perhaps to produce local anæsthesia of the mucous membrane of the mouth and head, for example, and even for this purpose bromide of potassium and tannin are less injurious.

Dosage and Preparations.—1. Semen colchici, given in doses of from 0.5 to 0.2, in powders, pills or infusion; the seed, however, is less often used than its preparations.

2. Tinctura colchici, given internally, 10 to 40 drops pro dosi (ad. 2.0 pro dosi! ad. 5.0 pro die!) alone, or as an addition to other medicines.

3. Vinum colchici, dose, the same as of the tincture (ad. 2.0 pro dosi! ad. 5.0 pro die!).

4. Acetum colchici, from 3.0 to 10 pro dosi.

5. Oxymel colchici, from 5.0 to 15.0 pro dosi.

6. Colchicinum, dose from 0.001. to 0.00.2; best given hypodermically.

Treatment of Colchicine Poisoning.—If in the usual mode of poisoning by preparations of colchicin taken into the stomach, vomiting and diarrhœa have not already commenced, evacuation of the stomach is of course to be effected; tannin should be given as a chemical antidote. In the later stages the violent vomiting and diarrhœa generally demand special treatment, which is made in the usual manner with ice, opium, etc. Other appearances, likewise, must be treated symptomatically, according to general principles.

THE ALKALOIDS OF BELLADONNA, JAMESTOWN WEED AND HENBANE.

The alkaloids of belladonna (atropine, belladonnine), of Jamestown weed (daturine) and of henbane (hyoscyamine, sikeranine) as well as duboisine, are very similar both in chemical composition and in their physiological action

on the pupils, heart, and salivary glands. They all distend the pupils and paralyze the mechanism of accommodation, the inhibitory apparatus of the heart, the splanchnic inhibitory fibres, the nerves of salivary secretion; but the doses of the various alkaloids necessary to produce these effects vary somewhat. We will therefore give minute consideration to atropine, which has been most accurately investigated, and a much shorter account of the others, omitting belladonnine entirely. Atropine, belladonnine, daturine, hyoscyamine and duboisine may all be considered as atropine, in which the remaining replaceable hydrogen atom has been replaced by the residue of an acid called tropinic acid, or, as was formerly supposed, belladonnic, daturic, and hyoscyamic acids respectively. Hyoscyamine, daturine and duboisine, however, are identical, according to Fadenburg, and should therefore be designated by a single name, preferably hyoscyamine, although they are derived from different plants. Atropine, on the contrary, is not identical with hyoscyamine, but is isomeric with it and yields the same products of decomposition. The acids formerly described as hyoscyamic, daturic, etc., do not differ from tropinic acid.

Hyoscine is identical with tropin. Fadenburg states that he succeeded in synthetically producing artificial atropine, identical with the natural alkaloid, and also the products of decomposition of hyoscyamine, by treating the products of decomposition of atropine (tropine and tropinic acid) with dilute hydrochloric acid at a temperature below 100°. He therefore succeeded in converting, by a circuitous route, hyoscyamine itself into atropine. How the isomerism of atropine derived from belladonna and hyoscyamine derived from hyoscyamus, datura and duboisia is to be regarded, is not definitely decided by Fadenburg's researches. Perhaps they should be considered as merely physical isomers. According to the investigations of Fraser, Hellmann, Buckheim, and F. Eckhard, tropine, which is one constituent of all these alkaloids, does not possess the property of dilating the pupil at all, even when given in large quantities, and only to a very slight degree that of paralyzing the vagus and spinal cord. It obtains the former property and is strengthened in the latter only by the replacement of one of its hydrogen atoms by a molecule of tropinic acid. According to Fraser, atropine retains its action on the pupils and vagus when combined with an alco-

holic residue, but loses its other effects. All this forms a promising commencement for a future knowledge of the relation between physiological action and chemical composition.

ATROPINE AND BELLADONNA.

Atropine, $C_{17}H_{23}NO_3$, present in all parts of the belladonna plant (atropa belladonna), forms fine white prisms with an unpleasant, sharp, bitter taste. It dissolves in 58 parts of hot, 300 parts of cold water; is very readily soluble in alcohol; and is readily decomposed in solution even when combined with acids. It is also decomposed on heating. Solutions of baryta separates it into tropine and tropinic acid (Fossen). Atropine into tropin and tropinic acid, $C_{17}H_{23}NO_3+H_2O=C_8H_{15}NO+C_9H_{10}O_3$. Hence we may regard atropine as tropine in which the replaceable hydrogen atom is replaced by the residue of tropinic acid. Tropine is isomeric with vinyl—diacetonamin (Heintz). There also seems to be a close connection between collidin ($C_8H_{11}N$), tropidine ($C_8H_{13}N$), and conicin ($C_8H_{15}N$), tropinic acid ($C_9H_{10}O_3$), is very readily converted, by loss of water into atropinic acid ($C_9H_8O_2$). The latter is isomeric with cinnamic acid and, like it, yields benzoic acid upon oxidation. The proportion of atropine in different plants of belladonna and different parts of the plant varies between 0.06 and 0.3 per cent (Günther, Procter).

PHYSIOLOGICAL ACTION.

The action of the belladonna plant is that of atropine, but, of course, much weaker. It is therefore unnecessary to consider belladonna alone. Different animals show uncommonly great differences in their sensibility to the action of the alkaloid. Man is most affected by atropine. Doses as small as 0.005 grm. produce symptoms of violent poisoning; 0.1 grm. may be considered a fatal dose. Herbivora, on the contrary (Guinea pigs, rabbits, asses, horses, and doves), resist its action to a great degree.

Rabbits are able to feed entirely upon belladonna leaves for weeks without being dangerously affected, and in many of them the dose of atropine necessary to produce death is 1.0 grm., ten times the fatal dose for men. It follows that men may be severely poisoned by eating the flesh of these animals, which, as they are not affected by atropine, may be impregnated with belladonna. In certain animals, *dogs for instance*, a faculty of becoming habituated to increasing doses of atropine is shown (Anrep).

ABSORPTION AND EXCRETION.

Atropine is taken into the blood through all mucous membranes and the subcutaneous connective tissue, but not through the uninjured skin. It very quickly reaches all organs in which its presence can be demonstrated, and is very soon excreted with the urine unchanged, so that in from ten to twenty hours after atropine has been taken, it has deen entirely excreted (Dragendorff, Schmidt). In the herbivora it is least retained by the organs and seems to leave the body most quickly, as may be inferred from the rapid disappearance of many symptoms of poisoning, such as paralysis of the vagus.

This indeed is one of the causes of its harmlessness to these animals. Atropine can be detected in decomposing organic tissues for two and one half months (Dragendorff).

Poisoning by Atropine.—Small doses produce symptoms of poisoning very quickly; instantly upon direct injection into the blood; in two or three minutes after hypodermic injection; in five to ten minutes after it has been applied to a mucous membrane or taken into the stomach. We describe here only the symptoms that appear in men, chiefly the results communicated by Schneller and Flechner, of the experiments made by 16 Vienna physicians upon themselves with different preparations of belladonna.

We also give the experiments of Fusanna, Schroff, Lichtenfels and Froelich with atropine. The particular effects, both on men and animals, we consider under the particular organs.

After small or moderate doses of atropine (0.003 to 0.02 grm.) the first effects are: Dryness and a scraping sensation in the mouth and throat, difficult deglutition, hoarseness, difficulty in moving the tongue, nausea, inclination to vomit, increased pulse, followed by diminished frequency of the pulse, pressure in the supra-orbital region, vertigo, pain radiating forward from the occiput, various disturbances of sight, such as cloudiness, vision of colors and diplopia, dilatation of the pupils, redness of the conjunctiva, delirium, sometimes of the quiet, sometimes of the active form, destructive impulses, choreic movements, vesical tenesmus, redness and dryness of the skin and œdema. After very large doses (0.05 to 0. 1 grm.) all these symptoms are increased to an extraordinary degree. Secretion of saliva

ceases entirely; swallowing becomes impossible. In the experiments hitherto made there appeared general convulsions resembling those of hydrophobia, entire loss of speech and voice, accelerated gasping respiration, general trembling, increasing to clonic contractions of the muscles of the face and the extremities, dry, hot, and scarlet skin.

This state of extreme stimulation is followed immediately by loss of consciousness and sensation, paralysis of the muscles of the extremities, rattling respiration, weak, irregular, and retarded action of the heart, involuntary escape of urine and fæces, and death.

EFFECTS ON INDIVIDUAL ORGANS AND FUNCTIONS.

The activity of the brain is at first stimulated to the highest degree. The symptoms of vertigo, the strong hallucination and delirium increasing to violent attacks of maniacal rage, accompanied by great development of muscular strength, can only be produced, as von Bezold thinks, by the removal of certain inhibitory functions. It may also be supposed that the inhibitory control of consciousness and will suffers from the effects of atropine in the same manner as the inhibitory apparatus of other organs, as the heart for example, and that the condition of intoxication above described and the peculiar incitement to motion depend, not upon stimulation of the brain, but upon paralysis of those organs in the brain that control the passions and the motor functions. But, unfortunately, neither do we certainly know of any such inhibitory organs in the brain, nor does Bezold's theory rest on any proof. On the contrary, Bezold himself found in dogs and rabbits another and well demonstrated inhibitory centre in the brain, namely, that of the origin of the vagus, was stimulated (see below) so that his conclusion above referred to is not strictly analogical. After this state of mental excitement has lasted for a time it changes into the opposite condition, as after the action of all intoxicating poisons. Weariness is followed by constantly deepening sleep, which, if the dose is large, increases to sopor and coma, in which the patient, deprived of consciousness, sensation, and motion, and incapable of being aroused, gradually passes away.

The reason that atropine and belladonna, though similar *in effect to the* intoxicants, alcohol, opium, hasheesh, etc., *is not used like these* as an habitual stimulant is manifest-

ly the exceedingly unpleasant effect of atropine on the mouth and heart. The insatiable thirst arising from arrest of the ordinary secretions, and the greatly increased frequency of the pulse, produce, even in the stage of stimulation, a painful rather than the pleasant condition caused by other intoxicants.

The effect of atropine on the *spinal cord* is not yet sufficiently clear.

Still, we think, judging from our observations on warm-blooded animals at least, that we do not err in describing the initial effect as an increase of reflex irritability, the final effect as paralysis of the same.

The convulsions that sometimes take place towards the end of life, after symptoms of general paralysis have long been present, must be ascribed not to atropine, but to accumulation of carbonic acid in the blood and regarded as convulsions of suffocation.

In cold-blooded animals, on the contrary, the first effects are paralysis of the spinal cord and brain, failure of voluntary and respiratory motions and general paralysis of reflex actions. Frogs lie for two or three days as if dead, the only signs of life being the continuance of pulsations of the heart and direct muscular irritability. Tetanic condition does not occur until after the gradual return to consciousness (Fraser).

Peripheral Nerves and Striped Muscles.—In cold-blooded animals the irritability of the *sensory* nerves is not diminished by atropine, except in very large doses. Even this unimportant action is not quite certain of occurrence (Bezold and Bloebaum).

In dogs, increase of sensibility is shown at first (Anrep). In men pain has been observed to disappear under the direct action of atropine, for example, after application of belladonna ointment to painful fissures, and after hypodermic injection.

The *motor nerves* of the frog are not paralyzed unless they receive large quantities of the poison. The paralysis seems to first affect the intra-muscular terminations, and afterwards the trunk of the nerve.

This drug, however, cannot be classed with curare in this respect, as much larger doses of atropine are required, and all the other organs are poisoned long before this effect on the nerves takes place, and as this action never occurs in mammals after introduction of atropine into the

blood, but the motor nerves and the muscles retain their irritability (Von Bezold).

The Nerves of the Eye and Pupil.—Dilatation of the pupil and paralysis of the mechanism of accommodation follow both the application of the drug to the conjunctiva and general atropine poisoning. When atropine is dropped upon the conjunctiva, stimulation of the latter is observed in many instances. This arises chiefly from the solution being not carefully neutralized, or being somewhat impure, as all individuals to whom a particular solution is applied show symptoms of stimulation, whereas these symptoms disappear if another solution is employed. The contraction of the pupil which precedes the dilatation, first observed by us in rabbits, and afterwards noticed by other observers in men, may also proceed from the same stimulating action (from a reflex transmission arising from stimulation of the sensory fibres of the trigeminus). If the introduction of such stimulating solutions is continued for some time, a catarrhal affection of the conjunctiva, so-called follicular catarrh, sets in. The dilatation of the pupil is greatest in men, cats, and dogs. It is so great that but a narrow rim of the iris remains visible. In birds there is no dilatation whatever (Kieser). Exceedingly small quantities, 0.0001 grm., according to Graefe, even 0.0000005 grm., according to De Ruiter, are sufficient to cause prolonged dilatation. According to all investigators, without exception, the dilatation is caused chiefly by paralysis of the terminations of the motor oculi in the iris itself (E. H. Weber, De Ruiter, Gruenhagen, Hirschmann, Bezold and others), not by paralysis of more remote centres or of those in the brain. This is shown by the production of partial dilatation, after affecting only a small part of the iris, when very small quantities of the poison are carefully applied to a single point (Flemming).

In the stage of maximum dilitation, therefore, contraction of the pupil cannot be brought about by stimulation of the exposed motor oculi or by stimuli conveyed reflexly through the ciliary branch of the motor oculi—as the impression of light, for example. The spincter muscle itself, on the other hand, retains its contractility under direct stimulation for a longer time (Bernstein and Dogiel and others). Very large doses and long action are required to *destroy* its susceptibility to stimulation (De Ruiter). Cra*mer, Donders, and* De Ruiter are of the opinion that stimu-

lation of the terminal branch of the sympathetic in the dilatator pupillæ, produced by atropine, also contributes to the maximum dilatation. This view is supported by the fact that complete interruption of communication in the trunk of the motor oculi produces only semi-dilatation of the pupil, and causes no noteworthy symptoms of strain in posterior synechiæ, while atropine dilates the pupil to the utmost, and produces visible tension and frequent laceration of posterior synechiæ, as well as great knotty expansion of adherent segments of the edge of the pupilary margin (Stellwag).

It is further supported by the statement of Schur that the pupil of a rabbit's eye treated with atropine contracts to 1 or 1.5 mm. after the cervical sympathetic has been severed or the ganglion supremum destroyed. Other statements made to support this second view, for instance, that a pupil dilated by atropine cannot be further dilated by stimulation of the cervical sympathetic or even by direct stimulation of the iris, are less certainly proven as well as less conclusive. Many investigators consider it impossible to fully reconcile the facts while the terminations of the motor oculi are paralyzed; those of the sympathetic are not affected or even are stimulated. Bezold obviates this difficulty by interpolating hypothetical intermediate ganglia between the motor oculi and the sphincter of the iris, while, considering the sympathetic to terminate directly in the dilator. It is then only necessary to assume that both the motor oculi and the sympathetic remain intact, and that only the intermediate ganglia of the motor oculi are paralyzed, in order to explain, without difficulty, all the symptoms of mydriasis. All these difficulties, however, are again met with in the action of atropine in the heart and intestines. We ourselves regard the whole question as still far from solution, and therefore omit any further discussion of explanations of this character.

A consequence of the dilatation of the pupil is blinding by the admission of too much light. Paralysis of the mechanism of accommodation occurs somewhat later than the dilitation of the pupil. It is always to be ascribed, however, merely to paralysis of the ciliary branch of the motor oculi. The ciliary muscle can no longer affect relative motion of its two points of attachment, the edge of the iris and the choroid, and hence can no longer change the curvature of the anterior surface of the lens (as the

sight is directed to nearer or more remote objects). The symptoms of this loss of the power of accommodation differ, of course, according to the character, i. e., the natural focus of the eye. A normal (emmetropic) eye, when accommodation is paralyzed by atropine, still sees distant objects very well (since, in this case, the eye is normally in a state of repose), but cannot see near objects with distinctness.

The vision of a myopic eye is less affected the greater the degree of short-sightedness, for its distant limit of vision is not changed, so that it can still see distinctly at that distance. Hypermetropic eyes, i. e., those whose focus for parallel rays is behind the retina, are most affected, and require the aid of convex glasses in order to perceive distant objects. The effect upon the intraocular tension has not yet been studied with great exactness. It is, indeed, increased by very concentrated doses (Gruenhagen), purely in consequence of the above-mentioned stimulating action. Whether the solutions commonly employed have a similar effect is still to be investigated.

The substance of the *striped muscles* of the trunk and extremities retains its irritability uninjured in atropine poisoning, both in cold and in warm-blooded animals (von Bezold).

When the poison, however, is injected directly into the muscle through one of its vessels, the maximum contraction decreases much more rapidly and life of the poisoned muscle is much shorter than in the case of the normal comparison muscle, even when the dose of atropine is very small (Rossbach).

The frequency of respiration is somewhat diminished at first, as the first action of the atropine which circulates in the lungs is to paralyze the sensory fibres of the pulmonary branch of the vagus and hence removes the impulse to respiration. Subsequently the quantity of poison in the brain increases, and that in the pulmonary circulation correspondingly diminishes. In consequence of this the irritability of the pulmonary branch of the vagus appears to recover, and at the same time, stronger stimulation of the respiratory centre in the medulla oblongata appears to be caused by the gradual increase of poison in that part. Respiration then is strongly accelerated. This acceleration occurs whether the blood-pressure is high or low, so that we cannot suppose that the increase in frequency is caused by failure of oxidation due to reduced circulation. The

greatest acceleration occurs when the greatly reduced blood-pressure begins to recover. As respiration becomes more frequent it becomes more superficial. Stimulation of the central end of the vagus and of the superior laryngeal nerve, however, has the same effect on poisoned as on normal animals (Keuchel).

The greatest doses finally cause paralysis of respiration and death (von Bezold). The hoarseness and loss of voice often observed may proceed from dryness in consequence of the total cessation of the secretion of saliva and mucus and the simultaneous increase of frequency of respiration.

Influence on the Circulation and Vagus—After very small, and in the commencement of the action of larger doses of atropine there occurs, most frequently in men, but also in animals (frogs and rabbits), a transient diminution in the frequency of the heart's beat. This period of diminution in men is shorter, the larger the dose of atropine. In frogs long diastolic pauses may even occur. The diminution is caused by an initial stimulation, partly of the vagustonus in the brain, partly of the inhibitory apparatus in the heart itself. On account of the objections made to this view by Harnack, we here give the names of all trustworthy observers who have confirmed by observation and experiment the slowing of the pulse as well as the increase of vagustonus in the brain and heart. These are Seneller and Flechner, Werthheim, Lusanna, Schroff, Lichtenfels and Froehlich, von Bezold and Bloebaum, Rossbach. While, however, this initial slowing of the pulse is always very transitory, and often does not occur at all, the enormous acceleration of the heart's beat, greatest in men and dogs, less in cats, the normal frequency of the pulse being doubled or trebled, and the simultaneous increase of blood-pressure, are among the most characteristic signs of atropine poisoning. The acceleration of the heart's beat by atropine entirely resembles that produced by severing the vagus in the neck, and is caused by paralysis of the extreme ends of the vagus in the heart (von Bezold and Bloebaum, Schmiedeberg). The acceleration is greater in proportion to the strength of the previous inhibition, and the acceleration by atropine may be regarded as an accurate measure of the strength of so-called vagustonus. In rabbits and frogs, for example, under normal conditions, no stimulation reaches the heart through the fibres of the *vagus; there is* no vagustonus, for which reason atropine is

unable to accelerate the heart's beat (this may give a further explanation of the fact that herbivora are comparatively little affected by atropine).

In this stage of poisoning even the most violent stimulation of the cervical vagi is unable to diminish the frequency of the heart's beat. On the contrary, Keuchel and Bidder in many cases observed a still greater increase of frequency as a result of this stimulation. This they correctly ascribed to the fact that only the inhibitory fibres were paralyzed while the accelerating nerves of the heart retained their irritability under the doses employed. The increase of blood-pressure that occurs simultaneously with the increase in frequency is due partly to stimulation of the vaso-motor centre, causing active contraction of the smaller peripheral arteries, partly to the increased frequency of the heart's beat. The heart's beat, indeed, though enormously accelerated, is not weakened at all by small doses. This characteristic action on the extreme ends of the vagus in the heart is produced in full-grown dogs, cats, and men, by a dose of 0.001 grm. in the mean. If the dose is increased, all the other parts of the circulatory apparatus are successively affected in the same manner. The irritability of the vaso-motor centre, at first increased, becomes by degrees more and more reduced so that the contracted peripheral arteries again dilate and the increased blood-pressure is constantly diminished. The excito-motor ganglia of the heart, though remaining long unaffected, are likewise rendered less irritable and finally paralyzed by large doses of atropine.

The initial acceleration of the pulse was the direct expression of impulses proceeding from these ganglia, and through their gradual paralysis the pulse continually becomes slower and the contraction of the heart weaker. There is also a diminution of the irritability of the muscle of the heart itself, and so finally the heart stops in diastole, paralyzed in all parts and dead (von Bezold and Bloebaum). In consideration of the great physiological importance of atropine on the one hand and of the vagus on the other, we deem it useful to briefly collect in this place those effects of the alkaloid upon the different fibres that have thus far been certainly proved by experiment. By very *small* doses (0.001 grm. on the average) the sensory fibres *of the pulmonary* branch of the vagus are paralyzed in *their peripheral* expansion, and the extreme peripheral ex-

tremities of the inhibitory fibres of the vagus in the heart are paralyzed after brief initial stimulation (von Bezold). After these doses the fibres running through the trunk of the vagus itself, however, both the centripetal fibres from the lungs and larynx and the centrifugal inhibitory fibres, retain their irritability unchanged. The accelerating nerves of the heart which run through the trunk of the vagus, as well as their extremities in the muscle of the heart, also remain irritable (Keuchel, Schmiedeberg). Finally, the vaso-motor fibres which go to the abdominal organs retain their irritability (Rossbach). To paralyze the last in dogs requires the introduction of more than 0.008 grm. of atropine into the body. The dose required to paralyze the other fibres is not exactly determined. The action of the inhibitory fibres of the nervi depressores terminating in the brain, in reducing the blood-pressure, is not affected by atropine (Keuchel). The temperature of the body is increased by small but always decreased by large doses. It is not difficult to deduce these effects from the disturbances in respiration and circulation.

Digestive Apparatus.—The dryness in the mouth and throat is perhaps partly due to the absence of secretion of mucus, but chiefly to the entire cessation of the secretion of saliva. The minute investigations of Keuchel, and especially those of Heidenhain, have shown that paralysis of the secretory fibres of the spinal cord, or rather of a (not yet demonstrated) ganglionic apparatus connecting the salivary glands and the terminations of these fibres, is the cause of the arrest of salivary secretions. They have shown, further, that the dilating fibres in the cord, which supply the salivary glands, as well as the secretory fibres of the sympathetic which are connected with the same glands, remain uninjured and are not paralyzed. While, therefore, in atropine poisoning, stimulation of the cord produces no trace of salivary secretion, it causes, as in animals in normal condition, acceleration of the current of blood in the veins, so that bright red blood spurts from the vein at each beat of the heart, often with great force. Stimulation of the cervical sympathetic produces secretion of saliva as well after as before poisoning. Michel furthermore has made the interesting statement, of the truth of which we have assured ourselves by several experiments, that in cats the introduction of small doses of atropine, or *even such as* are sufficient to produce mydriasis, into the

conjunctiva, always causes profuse secretion of saliva. Of the effect on the *stomach* and *intestines* we know only that nausea and vomiting are frequently produced by atropine poisoning. Nothing whatever is known concerning the influence on the bile and other secretions of the abdominal viscera. We have, however, the results of investigations concerning the effect on the fibres of the vagus and splanchnic which supply the abdominal organs.

The vascular nerves of the vagus which go to the stomach and intestines remain irritable after relatively large doses of atropine, and are not paralyzed (in dogs) unless the dose is as large as 0.008 grm.

This is the cause of the remarkable phenomenon that stimulation of the cervical sympathetic, at a time when all the inhibitory nerves of the heart are paralyzed, produces increase of blood-pressure despite the unaltered action of the heart, because contraction of the vessels controlled by the abdominal branch of the vagus still occurs (Rossbach and Quellhorst).

The statements of von Bezold and Keuchel, concerning the intestinal ganglia and the splanchnic nerve are widely at variance. We have therefore submitted the matter to further experiment, and are compelled to confirm Keuchel's statements that in rabbits, after small doses of atropine, the activity of the intestinal motions increases (von Bezold states that it decreases); also that the nervi splanchnici lose their inhibitory influence upon the centres of intestinal peristaltic motion. The effect upon the nervus splanchnicus is therefore remarkably like that upon the vagus as in the former; just as in the vagus the inhibitory fibres are paralyzed even by the smallest doses, at a time when all other nerves, and even all the other fibres (sensory and vasomotor) of the splanchnic nerve itself, still retain their efficiency. Severing the splanchnicus, in fact, even after atropine poisoning, causes marked expression of pain and fall of blood-pressure, while stimulation of its peripheral extremity produces an important rise of thelatter (Keuchel.) We have not investigated whether very large doses of atropine also finally paralyze the motor ganglia of the intestines (von Bezold).

There are no close and reliable observations concerning the secretion of urine. Gray found it increased; Harley *found an increase* in the secretion of nitric, sulphuric, and

phosphoric acids, and a diminution of the chlorides in the urine.

The *skin* grows hot, red, and dry; after giving the smallest doses perspiration ceases entirely and cannot again be brought on by exciting the nerves controlling perspiration (Lucksinger).

The death from atropia is caused by paralysis of the heart.

THERAPEUTIC APPLICATION.

The number of conditions of disease in which atropia and belladonna are resorted to is naturally exceedingly great, as in all powerful remedies. We believe that we are justified in stating that atropia is only absolutely reliable and indispensable as a mydriatic. It often proves useful in cases in which it is necessary to limit an abnormal secretion of saliva or perspiration. Occasionally it has been found of some value in conditions where the effect of an influence upon the sensitive nerves can be diverted. In almost all these conditions, however, morphine is absolutely the safer and more reliable drug. In other isolated troubles it is but very rarely effective.

In ophthalmology atropia is one of the most indispensable remedies. Its application is for explorative and curative purposes.

In the first instance it is used to facilitate ophthalmoscopic examination by dilating the pupil, especially if the latter be exceedingly small or if there be simultaneous opacities of the refractive media; again in examination by oblique illumination, preferably for the more certain diagnosis of opacities of the lens.

In order not to have the pupil dilated for too long a time, weak solutions are employed; a drop of the ordinary solution (atrop. sulf. 0.05 : 2.0 to 3.0 aquæ to the teaspoonful of water) suffices, provided the margin of the iris be free. Furthermore, atropia is used to exclude accommodation entirely, in order to ascertain the degree of error of refraction. In this case a strong solution is necessary to completely paralyze the ciliary muscles.

Far more manifold is its application for curative purposes.

Although atropia has proven so important and indispensable in ophthalmology, nevertheless its application *must be attended* with caution; and since an instillation of

atropia is capable of creating an attack of glaucoma, which appears very suddenly without exception, commonly after a few hours, and varies in intensity. Such an effect of a single instillation of atropia is chiefly prone to occur when the intra-ocular tension is on the border-line of the normal—when a glaucoma is about to develop. In all such cases, therefore, where this can be discerned, the application of atropia is contraindicated; indeed it does not even appear admissible, be it to obtain a larger area of the pupil, in cases of opacities of the lens, nor in ophthalmological examinations to test the refraction, nor be it for therapeutic purposes.

For therapeutic purposes atropia is employed in such diseases of the cornea in which we have to deal with superficial lesions which come on with strong photophobia—in short the so-called stage of irritation—or in which a simultaneous participation of the iris is already present, or to be warded off prophylactically, as in keratitis parenchymatosa.

Atropia is contraindicated in cases of deep ulceration of the cornea in which there is danger of perforation, and in those which come on with an increase in the intra-ocular tension. Should atropia be employed in such a case, we would find, besides the ulcerations, an unusually rapid necrosis of the cornea.

The most important application of atropine is in the diseases of the iris; hence to avoid disease of the latter we instill atropine as a prophylactic; and where in a surgical interference, as in extraction of a cataract or discisions, there is any possibility of the iris or the border of the pupil participating or being mechanically irritated by remains of the lens. In acute and chronic iritis we rend asunder the posterior synechia, i.e.. the adhesions between the border of the pupil and the anterior surface of the lens-capsule. In a number of cases where the inflammatory stage is past, we often alternate physostigmine and atropine. More frequently is this done in adhesions between the iris and a scar of the cornea, the so-called anterior synechia. The majority of observers note that after atropinization the field of vision is increased; recently the contrary has been claimed (Färber).

In order to obtain a regular effect we must see to it that the instillation be not made too often, but at regular intervals. These intervals depend upon the anatomical changes *in each individual* case. In progressive myopia of youth, *so-called, the* atropine treatment is recommended, and it is

of decided value, as is evidenced by the fact that the progress of the myopia is arrested for a long time at least.

More recently atropine has been recommended in morbid perspiration, viz., in phthisical subjects (Sidney Ringer, Fräntzel and others). Of course it often disappoints, but we must state from our own experience that it is most decidedly more effective than all those remedies hitherto used for this evil symptom. At times the night-sweats of phthisical subjects are relieved; sometimes with surprising rapidity, but it is only for a time. Ebstein employed it in abnormal salivation, viz., in cases of hemiplegia, and achieved a transitory relief of the same. Extensive experience must teach us under what particular circumstances a result is to be expected. We employed it without any great effect in a case of extensive secretion of saliva in an old man for which no cause whatsoever, especially no disease of the buccal cavity or of the salivary glands. could be discovered; and also in a case of salivation in a hemiplegic patient.

Atropine, or rather belladonna, and its preparations are furthermore given in conditions in which the therapeutic value can be ascribed to a diminution in the morbidly increased excitability of the peripheral sensitive nerves, no matter whether the latter exhibits itself as pain or as reflex by the phenomenon of motion. It cannot be denied that it is of value under such circumstances. There is no doubt, however, that in all these cases the efficacy of morphine and of the preparations of opium is decidedly more reliable; consequently we do not, for the sake of simplifying therapeutics and other medical matters, hesitate in selecting morphine in preference to atropine to fulfil these indications. However, to fulfil our purpose we will state the more essential conditions in which the latter is often chosen.

Cardialgia, whether dependent upon anatomical lesions of the stomach (ulcer, etc.) or not. It often relieves the intense pain when applied externally to *fissures of the anus*. *In neuralgias* belladonna is often given as a soothing remedy, most frequently in trifacial neuralgia, also in sciatica and other forms of neuralgia. These reports are in part not clear, as other remedial means were simultaneously employed (vesicants, etc.); but in part it is evident that belladonna exerts but a slight effect; only Béhier claims to have seen more benefit in subcutaneous injection of atropine in cases of sciatica than in the use of other remedies. Nevertheless, an abatement of the pain is to be

noticed only upon the appearance of the symptoms of intoxication. The external application in neuralgia is of just as little established success as the internal use. Besides, belladonna is employed externally as a *local anodyne* in painful tumors, in rheumatic pains, and under other circumstances; its importance, however, is inferior to that of chloroform, moist heat, etc. Sometimes, to mitigate the painful introduction of a catheter, it has been smeared with belladonna ointment.

Among the other set of cases in which an exaggerated excitability of the sensitive nerves is manifested by excessive reflex action, belladonna has proven of great value, but also here it must cede the palm to morphine. In violent fits of coughing, the particular conditions for its employment are the same which we have given for morphine. Here also belong certain cases of so-called nervous or spasmodic asthma in which belladonna is applicable for the purpose of diminishing the cough. Perhaps, therefore, the well-known effect of belladonna in whooping-cough is accountable. Many careful experiments, which we can confirm, have established that belladonna does not abbreviate the duration of the disease, and, furthermore, that it is quite inefficient during the first weeks. Only towards the close of the disease it is said to alleviate the severity of individual attacks. The last-named advantage would thus be the most that could be expected, although we sometimes do not find this verified in practice; we cannot speak of a cure in tussis convulsiva. Old observers hold that belladonna should never be given in the acute catarrhal stage of whooping-cough, but only during the real spasmodic period, and recent writers claim that the remedy should never be administered to well-nourished (plethoric) children, especially if there be any signs of any active or passive hyperæmia of the brain. At times it is of great value in vomiting, whether it appears as a symptom of chronic structural change in the stomach (ulcer) or the so-called "nervous vomiting" (hysteric, anæmic) or the vomiting of pregnancy. Belladonna is often used externally with good results for *spasmodic stricture of the anus*, as it often appears in consequence of a fissure of the anus. In like manner accoucheurs use it in spasmodic stricture of the neck of the uterus during labor, which vanish after the local application of the belladonna ointment; others,

again, have not observed this. The special indications for each individual case are still wanting.

Belladonna is highly recommended by Bretonneau and Trousseau in chronic habitual constipation; but the precise conditions under which a result is to be expected cannot be put forth. Since this is confirmed by other observers, we may test the recommendation of the aforementioned experienced physicians.

In *epilepsy*, belladonna has been very much recommended by the older physicians (Theden, Stoll, Hufeland), whereas, more recently, atropine (Scoda, and especially many Italian physicians, and Trousseau also) has been indorsed. The more exact determination of the conditions in which it is really effective cannot be ascertained from present experiences. In a few instances we have noticed, upon subcutaneous injection of atropia, in old cases, without any etiology whatsoever, attacks cease for months, but no positive cure results. The same is seen, with a few exceptions, in studying the individual observations of older physicians in regard to belladona (Stoll), only an improvement, not a cure, while recently various physicians claim to have seen complete cure with atropia. There is, however, a lack of an adequate number of individual cases to confirm this, the criticism of which alone will tend to give us an idea of their value. The same is true of the application of the remedy in *chorea* as in *epilepsy:* wherever there was cure during its administration, it seems we had to deal with acute cases, which run a favorable course of themselves. Michea and others have ascribed an extraordinary effect to atropia valerianicum, particularly, but this has not been confirmed. In some forms of *paralysis* belladonna has been recommended by a few authorities as capable of some good, particularly Brown-Séquard urges its use in pronounced paralysis of the spinal chord, when similar conditions prevail that would call for secale cornutum (q. v.). We possess no sufficient reports on this score. The observations of the older authorities (Schmucker and others) in regard to the curative effect of belladonna in hemiplegia are of no value whatever.

Lately, R. Weber reported that he employed the extract of belladonna, and in small doses, with very good success as an excitant in collapse, which appeared under various circumstances; as in the course of an ileotyphus with severe bronchitis (and peritonitis?) of a gastro-enteritis

(and peritonitis?) and of, as it appears, an intoxication o digitalis. Entirely disregarding Weber's theoretical ex planation, we must, above all, wait for further indors ment of the stimulating effect of belladonna before accep ing it as such.

Dosage and Preparations.—1. Atropinum pure is scarcely ever gi ve the doses are the same as these of sulphate of atropine (0.001 pro do ad 0 003 pro die!).

2. *Atropinum Sulfuricum* crystallizes in delicate, thin, shining pris n slightly soluble in water and alcohol. Internally and subcutaneo us the dose is 0.0005 to 0.001 pro dosi (ad 0.001 pro dosi! ad 0.003 pro d ie in powders, pills, aqueous and alcoholic solutions. As a collyrium 0.05 0.1 : 15.0 to 20.0.

3. *Radix Belladonnæ*, internally the dose is from 0.015 to 0.1 (ad 0 pro die! ad 0.4 pro die!) it may be given twice to four times a day, in i fusion, powders or pills.

4. *Folia Belladonnæ* contain a somewhat slighter amount of atropine hence larger doses may be given; 0.03 to 0.2 pro dosi (ad 0.02 pro dos ad 0.5 pro die!) and in the same forms as the root. For external use the roots and leaves are pulverized for ointment (i. e. 1 part: 6 to 8 part of lard) or in infusion (0.5 to 0.1 : 100).

5. *Extr. Belladonnæ* is of the consistency of the heavy extracts; it dissolves in water, with a brown, turbid discoloration, and is but slightly soluble in alcohol liquids; therefore it is not to be combined with tinctures. Internally the dose is 0.01 to 0.1 pro dosi (ad 0.01 pro dosi! ad 0.4 pro die!) in powders, pills, and drops. Externally in ointments 5.0 : 30.0 of lard; in ointments for eyes 0.1 to 0.5 : 5.0. In place of the collyria of extractum belladonnæ, which were formerly used, we now employ solutions of atropine.

6. *Unguentum Belladonnæ*, 1 part extr. belladon. : 9 parts ug't cerei.

7. *Tinctura Belladonnæ*, ad 1.0 pro dosi! ad 4.0 pro die!

8. *Emplastrum Belladonnæ*, 1 part fol. belladon. : to 3 parts constituens.

APPENDIX.

Hyoscyamine.—In hyoscyamus niger (solaneæ) we find a crystallizable and an amorphous alkaloid. The crystallizable hyoscyamin, $C_{18}H_{23}NO_3$ (Geiger and Hesse) is resolved upon boiling in baryta water, like atropine, into tropin and tropinic acid.

Physiological Action.—Hyoscyamine acts like atropine, only the dilatation of the pupil takes place and disappears sooner; one pole of the iris is always more affected, so that the dilated pupil has an oval shape (Wecker and Königstein).

The action of the amorphous alkaloid, as well as that of the so-called base *sikeranin*, that are found in hyoscyamus, is not yet known (von Buckheim).

As the physiological effects of hyoscyamine so also its therapeutic indications accord with those of atropine. In ophthalmology it is recommended in these cases in which a rapid and transitory dilatation of the pupil and paralysis of the ciliary muscles is desired.

Formerly great influence upon neuralgia (particularly trifacial neuralgia) was ascribed to hyoscyamus, in which it was given in the form o

Meglin's pills with oxide of zinc (Meglin, Valleix, and others). Recent experiments do not confirm this; hyoscyamus achieves no more than atropine and much less than morphine; still Oulmont joins with the older experiences. It was formerly given as a soporific and was again brought to light by Fronmüller. But in this regard it is of no value. In *epilepsy* Stoerck and others claim to have seen excellent results, whereas P. Frank did not notice this; then the remedy was brought into use particularly by Herpin, who prescribed it in combination wfth flowers of zinc. Careful trials of hyoscyamus alone (as by R. Reynolds) have shown that it is true that the same tends to diminish the frequency and violence of epileptic attacks, but it does not cause any permanent cure. Oulmont noticed lately some relief from its use in mercurial and senile tremor. *Externally*, hyoscyamus is entirely inactive.

Dosage and Preparations.—1. *Folia hyoscyami*, internally 0.05 to 0.3 pro dosi (0.03 pro dosi ad 1.0 pro die), in powders, pills, and infusion. 2. *Semen hyoscyami*. 3. *Extractum hyoscyami* is of the consistency of the thick extracts, of a greenish dark-brown color, soluble in water, rendering the solution brown and turbid. *Internally* the dose is 0.01 to 0.02 pro dosi (ad 0.2 pro dosi! ad 1.0 pro die!) in powders, pills, linctus, and mixtures. 4. *Oleum hyoscyami infusum*, of a greenish color, used externally. It acts only as a rich oil, and no other effect need be expected from it if rubbed on the intact epidermis.

5. *Emplastrum hyoscyami*, like emplastrum belladonnæ. 6. *Unguentem hyoscyami*. 7. *Hyoscyamin*, not officinal, should be given in the same doses as atropine *daturine*. The alkaloid prepared from the leaves and seeds of the Jamestown weed (datura stramonium, solaneæ) is identical with hyoscyamin (Ladenburg). The physiological effects resemble those of atropine, but according to von Schroff they are produced by smaller doses of the former. A description of the physiological action of daturin appears superfluous after the above-mentioned considerations. The same is true of its therapeautic application, but its use in asthma, in which disease smoking stramonium cigars is even now much prescribed, demands a few words. There is a long series of observations according to which it cannot be denied that smoking stramonium cigars has occasionally been surprisingly beneficial in cases of pure so called nervous asthma, in which the patients suffered violent paroxysms of dyspnœa, while there was no evidence of material changes in the respiratory and circulatory systems. Isolated cases also cited by Namias and others in which dyspnœic paroxysms with pulmonary emphysema in chronic bronchial catarrah, that had defied many other remedies, quickly disappeared as a result of smoking stramonium leaves. The beneficial effect, however, is transient in all cases, and the symptoms of poisoning, which are very apt to appear, greatly restrict the use of this procedure. The remedy must always be discarded, as soon as a slight feeling of vertigo appears.

Dosage and Preparations.—1. Folia stramonii, given internally, from 0.03 to 0.15 (ad 0.25 pro dosi! and 1.0 per die!), in the form of powders, pills, or infusion. Smoking the leaves (stramonium cigars) is serviceable only to habitual smokers. 2. *Semen stramonii*. 3. *Extractum stramonii*, given internally, from 0.01 to 0.05 (ad 0.1 per dosi! ad 0.4 per die!) in pills or drops. 4. *Tinctura stramonii*, of a yellowish-brown color, 5 to 15 drops 2 to 4 times a day. (Ad 1.0 pro dosi! ad 3.0 pro die!) 5. *Daturin*, not officinal. *Duboisin* prepared by Gerrard in London from the Australian tree, *duboisia myoporoides*, is identical with

hyoscyamine. Its qualitative action is like that of atropine, but it produces the same effects by the use of smaller doses.

Because of its identity with hyoscyamine on the one hand and its high price on the other, there is no reason for the introduction of this preparation into practice. If it has been recently prescribed it should be replaced by our old hyoscyan ine.

Treatment of Atropine Poisoning.—In cases of poisoning by atropine or by plants containing it the first object to be attained is the evacuation of the stomach in the manner described under morphine. As direct antidotes, tannin, animal charcoal, and iodine are recommended, so long as poison can still be recognized in the stomach. The use of these is not sufficiently established in practice. If symptoms of poisoning proceeding from absorption are present, the same symptomatic treatment must be adopted as with morphine. In addition, physostigmine, prussic acid, and morphine are recommended as physiological antidotes. The theoretical aspect of this question we have already discussed. In practice very few experiments have been made with physostigmine, none whatever with prussic acid. On the other hand we have a long series of communications which mention a beneficial action of the hypodermic injection of morphine in atropine poisoning. Since, however, many serious cases of atropine poisoning recover without morphine, and, in fact, without any treatment, and since it has not been proved that in a single case treated with morphine there was sufficient atropine in the body to necessarily cause death in the absence of antidotes, this question is at least undecided at present.

THE ALKALOIDS OF THE CALABAR BEAN, JABORANDI LEAVES AND THE TOADSTOOL.

The alkaloids of the Calabar bean, physostigmine of jaborandi leaves, pilocarpine, and of the toadstool, muscarine, are all similar in their actions upon the animal system, and stand in notable physiological opposition to the alkaloids of the preceding group (atropine and hyoscyamine), inasmuch as they stimulate those very organs and parts of organs which are paralyzed by the former group. They contract the pupils, diminish the frequency of the heart's action, or even stop it entirely; they provoke profuse salivation and so forth.

In consequence of this opposition many effects of the alkaloids of this group can be removed by subsequent treatment with atropine (hyoscyamine), or can even be converted into the opposite condition, that of paralysis (*unilateral* antagonism).

It is stated, moreover, by a great number of observers

that the paralysis due to atropine may be removed by the stimulating action of these alkaloids; that there is, therefore, a bilateral antagonism, and that one group of poisons can neutralize the effect of the other group, as plus cancels minus, or two waves in opposite phases produce rest. According to this theory fatal doses of atropine may be rendered harmless by physostigmine, for example, and fatal doses of physostigmine rendered innocuous by atropine. The results of our own (Rossbach) investigations on this subject, according to which there is no true bilateral physiological antagonism between two poisons, we have already collected in the introduction to the alkaloids. We present here only the rules which hold for the antagonism of atropine and physostigmine groups in their actions upon the sudatory and salivary glands and the pupils. (1) The nervous terminals in the sudatory and salivary glands are affected by the smallest doses (relatively) of the poisons in question (paralyzed by atropine, stimulated by pilocarpine and physostigmine). The gland cells, on the contrary, remain unaffected by such very small quantities. Atropine in very minute doses, therefore, checks the secretion of perspiration and saliva only by paralyzing the nervous apparatus of the glands; pilocarpine and physostigmine, on the other hand, in very small doses promote the secretion of perspiration and saliva only by the stimulation of the same nervous parts of the glands.

2. By relatively large doses of these poisons, both the nervous and the cellular parts of the glands in question are affected; large doses of atropine, therefore, check the secretion of perspiration and saliva, by paralysis of the cellular as well as of the nervous parts of the glands; large doses of pilocarpine or physostigmine promote these secretions by stimulating both parts.

3. Atropine, moreover, acts in the above described manner in much smaller doses than pilocarpine or physostigmine. In other words, all parts of the glands are much more sensitive to the former than towards the latter; so that the minimum and maximum doses of the first poison are to be taken considerably smaller than the minimum and maximum doses of the other two.

4. Small and large doses of atropine always overcompensate small and large doses respectively of pilocarpine and physostigmine.

5. *The effect of* atropine, therefore, always predominates

when small doses of atropine and of pilocarpine or physostigmine enter the body simultaneously, or one after the other, and the same is true of large doses. It is indifferent whether these relatively equal doses enter the general system or are merely applied locally. In these cases both groups of poisons always act in exactly the same sharply defined manner, small doses on the nervous, large doses on both the nervous and cellular parts of the glands.

6. Only when the nervous parts of the glands alone are paralyzed by a disproportionately small dose of atropine, large doses of pilocarpine or physostigmine may provoke very ephemeral secretion by stimulation of the hitherto unaffected cellular portions of the glands, and thereby give a false appearance of bilateral physiological antagonism.

7. The above is equally true of the pupils, so far as relates to atropine and physostigmine.

8. Pilocarpine, however, cannot by any method of application destroy the action of atropine on the pupils.

9. Muscarine stimulates precisely the same parts that atropine paralyzes; the latter, therefore, can neutralize the former, but the former cannot remove the effects of atropine (Schmiedeberg). Here, also, therefore, there is merely a unilateral antagonism.

PHYSOSTIGMINE, CALABARINE, AND THE CALABAR BEAN.

The Calabar bean (faba calabarca seu semen physostigmatis) is the ripe seed of one of the leguminosæ physostigma venenosum found in the southern hemisphere. Its most effective ingredient is an alkaloid, physostigmine (or eserine), $C_{15}H_{21}N_3O_2$, which Jobst and Hesse obtained as a mass of indistinct, colorless crystals, and Amédée Vée in crystalline crusts or rhombic laminæ. This result, however, was not reached by later observers (Duquesnel, Harnack, and Witkowski), who obtained it merely in the form of a clear syrupy, more or less orange-colored mass which became brittle on drying. It is slightly soluble in water, more easily in acidulated water, and very easily soluble in alcohol, ether, chloroform, etc., and can, therefore, be completely extracted from the beans by alcohol. Alkaline, and to a greater degree the acid solutions, both of which are at first slightly colored, become gradually reddened by products of decomposition. According to Harnack and Witkowski the Calabar bean contains a second alkaloid which they name calabarine, and which is essentially distinguished from physostigmine by its insolubility in ether as well as by its physiological action. Commercial specimens of physostigmine and calabar extract contain varying proportions of physostigmine and calabarine.

PHYSIOLOGICAL ACTION OF PHYSOSTIGMINE.

The contradictions found in the numerous experimental results of Fraser, Harley, Leuz, Vintschgau, Bauer, Laschkewitsch, Von Bezold and Goetz, Arnstein and Sustschinsky, Roeber, Boehm, Schiff, Heidenhau, Koehler, Rossbach, Damourette, and many others must be in a measure referred to differences in the preparations employed in the investigations, especially in view of the fact that the Calabar bean contains two substances that differ materially in their physiological action—physostigmine which paralyzes the nerve-centres, and calabarine, which stimulates the spinal cord. These substances are present in different proportions according to the preparation employed. All preparations, however, agree in all essential points in their action upon the eyes, salivary glands, respiration, heart, and intestines, and differ according to their varying percentages of physostigmine and calabarine only in this, that one tends to produce tetanus, and the other paralysis of the spinal cord. We have observed contradictory effects on the spinal cord even in the employment of the same preparation upon the same species of animal. In what follows we give a critical collation of the experimental results relating to physostigmine of Jobst and Hesse, Harnack and Witkowski. We treat calabarine separately in a brief appendix.

Intensity of Action of Physostigmine.—Cold-blooded animals are the least sensitive. From 0.002 to 0.005 grm. are required to kill a frog. Of warm-blooded animals, all of which show distinct symptoms of poisoning after doses of 0.001 grm. Cats are the most sensitive. From 0.002 to 0.003 grm. are required to kill a cat; a rabbit requires 0.003 grm., a dog 0.004 to 0.005 grm. The fatal dose for the human species is not known; but symptoms of poisoning appear when 0.0005 or 0.001 grm. has been given (Harnack). The fatal dose of the various calabar extracts and the bean itself is difficult of determination.

Methods of Entering the System, Subsequent Course and Excretion.—Physostigmine, absorbed by all mucous membranes and wounds, is found in the blood, liver, and other tissues, and is excreted with the saliva and bile; it has not yet been found in the urine (Laborde and Léven, Dragendorff and Pander). The symptoms of poisoning in the human species, in particular those shown in Fraser's experiment upon

himself, are after small doses; pain in the intestines, vomiting, dyspnœa, vertigo, and a feeling of great weakness; medium doses produce an increase of the symptoms mentioned, myosis, salivation, perspiration, spasmodic respiration and slowing of the pulse; according to Evans almost complete muscular paralysis and marked collapse.

The effect on the organs and functions of men and animals is, cardinally, the following:

Central Nervous System.—In cold-blooded animals the brain is first paralyzed without previous stimulation, so that the sensibility and the voluntary motions cease while the reflex actions still continue. After this respiration ceases, and still later, reflex sensibility ends. The brain, therefore, is paralyzed much sooner than the spinal cord. In warm-blooded animals extraordinary differences exist according to the species even with the reference to Harnack's physostigmine, so that a single description of the process of poisoning is impossible. In great part the central nervous apparatus (both sensory and motor) is paralyzed without previous stimulation; only in cats, guinea-pigs, and susceptible men, as for instance, epileptics, symptoms of violent stimulation appear at first. Cats run impetuously to and fro, make peculiar motions, partly without apparent motive, become frightened, and are very sensitive.

Guinea-pigs which have been predisposed to (artificial) epileptic fits by Brown-Séquard's method of wounding the spinal cord and severing the sciatic nerve suffer these attacks, frequently in extraordinary numbers, a few hours after physostigmine poisoning. An epileptic idiot took daily for three successive days 0.005 grm. of physostigmine, which enormously increased his epileptic fits, so that during one night they were repeated in an almost uninterrupted series, with scarcely a quarter of an hour's rest. Symptoms of psychical excitement also were noted. Possibly this first stimulation in the case of the above-mentioned animals and man is caused less by a direct affection of the ganglia of the brain and spinal cord than indirectly through the changes in respiration and circulation. The final paralysis, however, can only be regarded as a direct action.

Peripheral Nerves and Striped Muscle.—The motor-nerve terminations in frogs, according to Harnack, are not paralyzed by physostigmine; at all events not by dose of 0.02 grm. or less. On the other hand, Harley, Rieder, Fraser, Martin-Damourette, and ourselves, using quite

different preparations, have found after long poisoning a stage in which stimulus to a nerve ceases to call forth muscular motions. We must therefore leave this question undecided for the present. Nor is anything exact known concerning the sensory nerves of the frog or the sensory or motor nerves of warm-blooded animals.

The nerves of the eye and of the pupil are less affected by general physostigmine poisoning, but very strongly by dropping the alkaloid upon the conjunctiva. In from five to fifteen minutes after this is done the pupil begins to contract markedly. According to Bäuerlein, however, the pupil exhibits some reaction when a strong light is thrown upon it, even after the maximum myosis has set in.

Shortly after myosis has been established an increased facility with respect to accommodation begins (Keuchel succeeded in producing a marked shortening of the nearest distance of distinct vision, without a trace of myopia, by means of physostigmine). After this, true spasmodic accommodation begins, the order being the reverse of that observed with muscarine. The latter action lasts a much shorter time than the myosis, and entirely disappears in two hours. In albinos, during the spasmodic accommodation all visible changes are quite the same as in the case of the strongest natural accommodation for near objects, but somewhat more sharply marked. The ciliary processes are markedly advanced towards the axis of the eye, and the circular dark line representing the edge of the lens, seems even somewhat broader and more sharply marked than in natural accommodation. We ourselves (Rossbach) have seen mydriasis finally set in upon the termination of the myotic stage in rabbits when a prolonged introduction of very large doses of physostigmine into the eye was made. There is scarcely any further doubt that the contraction of the pupil and the spasmodic accommodation depend upon a contraction of the iris and the ciliary muscle, brought about by stimulation of the terminations of the motor-oculi nerve. Evidence of this is given by the well-assured and universally accepted law that atropine destroys the effect of physostigmine. Engelhardt's experiment, according to which the pupil, in the stage of greatest physostigmine myosis, dilates upon direct stimulation of the iris, is less conclusive. At all events, the sympathetic *and the dilatator* pupillæ are not paralyzed. Paralysis of *these is not, therefore*, as Fraser claims, the cause of the

contraction; since by stimulation of the cervical sympathetic the pupil, which has been contracted to 3 mm. by physostigmine, can be dilated to 8 mm. The contraction of the pupil, furthermore, is not so strong after the sympathetic has been severed as when it is uninjured. Larger doses have also a stimulating effect upon the sphincter of the iris. A further action of physostigmine is the very marked reduction of intra-ocular pressure even in normal eyes; also contraction of the orbicularis and unilateral hemicrania.

The striped muscles of cold-blooded animals are little affected by physostigmine, even when this is directly injected through an artery of the muscle. Upon direct stimulation after this treatment they do not differ essentially from normal muscles either in the form of the curves of solitary contraction or tetanus or in the duration and extent of muscular irritability. The prolongation of the falling part of the curve which is seen in individual physostigmine muscle-curves cannot be referred to the poison, for in the normal comparison muscles sometimes show the same phenomena (Rossbach). We have not been able to find any important increase of direct muscular irritability, as stated by Harnack. We have found, on the contrary, an increase in length of the muscle in consequence of the destruction by physostigmine of the tone of the muscle. We have also found increase of muscular elasticity due to the action in the contractile substance itself (Rossbach and Anrep). In warm-blooded animals violent fibrillary twitchings of all the muscles of the body often occur. Their first observer (Fraser) referred these to immediate stimulation of the substance of the striped muscles; but, according to Harnack, this is not clearly established, since upon poisoning with curare these motions caused by physostigmine gradually and completely disappear. In conclusion, since we and others have found the motor-nerve terminations in frogs paralyzed, though the muscular irritability was maintained (see above), it appears to us more probable that in warm-blooded animals the terminations of the muscle-nerves are first stimulated, and that the fibrillary twitchings are the expression of this stimulation.

The respiration is primarily accelerated in warm-blooded animals. According to Bauer, this is probably due to spasmodic action of the bronchial muscles; according to Brandt

and Goetz, to spasm of the bronchial muscles in response to stimulation of the peripheral terminations of the vagus nerve in the lungs; whence this initial acceleration does not take place after the vagi have been severed. In the end the respiration and its nerve-centre are paralyzed, so that the usual means of stimulating the latter, such as apomorphine, are ineffectual (Harnack), and the life of the animals can be sustained longer by artificial respiration (F. Bauer).

Circulation.—The heart of the frog beats more slowly after small doses (0.0005 grm.); after somewhat larger ones it stops in diastole. Simultaneously with the diminution in frequency the systole becomes stronger, the drawn curves not only higher and more prominent, but the upper points broader also; diastolic and systolic intervals often alternate (Rossbach). The action of the heart is likewise retarded in warm-blooded animals (rabbits, cats, and dogs), and the blood pressure rises at the same time.

These are the observations made by us in agreement with most other observers. It is very difficult to explain this action and to trace it back to the effect upon the separate nerves of the heart and chest, on account of our still very incomplete knowledge of the physiology of the heart. It is not our object in this place to follow out all the hypotheses that have been proposed, many of which are very artificial. We therefore merely observe that our own experiments lead to the conclusion that in cold-blooded animals there is a simultaneous strong stimulation of the inhibitory and musculo motor nerve-centres of the heart; in warm-blooded animals stimulation of the vagus takes place. Harnack, on the contrary, reasoning from the comparison of the heart's activity under the simultaneous action of various poisons (atropine, muscarine, etc.), ascribes to physostigmine a quite peculiar effect upon the heart-muscle itself in cold-blooded animals. For warm-blooded he leaves this point undecided.

The action of atropine, etc., upon the heart, however, is also within the realm of hypothesis at present. It is now generally admitted that physostigmine and atropine have no bilateral antagonism in their actions on the heart. This we were the first to prove. Here also belongs the noteworthy statement of F. Bauer that the veins of the mesentery of the cat are thrown into partial contraction by physostigmine, so that thread-like strictures alternate with *varicose expansions.* The temperature of the body gradu-

ually sinks in consequence of the effects upon the respiration and heart (H. Köhler).

Digestive Apparatus.—The secretion of saliva in dogs, cats, and men is increased for a time. This, according to Heidenhain, proceeds from stimulation of the central origin of the respective nerve. The current of blood in the glands is retarded by stronger doses, both because of excitation of the sympathetic vascular centre in the spinal cord and because of stimulation of the intra-glandular vaso-motor centre. By this means a complete interruption of the blood-current in the glands and, further, a complete cessation of secretion of saliva may be brought about; the latter being a consequence of the paralysis of the bloodless gland.

The entire intestinal canal from the stomach to the rectum is, as Bauer observed, first in rabbits and more markedly in cats, thrown into a violent tetanic convulsion, from which result nausea, vomiting, and frequent evacuations of watery fæces mixed with blood and mucus. Bauer, Westermann, Von Bezold, and Goetz attribute them to an irritation of the intestinal ganglia; Harnack ascribes them to an irritation of their muscles. During the spasm the intestines are pale and the mesentery shows the above-described contraction of the veins.

Bauer also observed an atrophy of the spleen.

Secretions.—Whether the perspiration and the tears and urine are increased is not known with certainty.

The cause of death is always the final respiratory paralysis (Harley, Bauer, and others).

There are, as is evident from the preceding, two views which are irreconcilably opposed to each other. According to the one, physostigmine acts upon the central and peripheral nervous systems, its influence paralyzing the central, and stimulating the peripheral at first and then paralyzing it. According to the other the central nervous system is indeed weakened, but the peripheral is not, or at least very slightly affected, but the substance of the smooth and striped muscles is excited.

THERAPEUTIC APPLICATIONS.

These may be confined to ophthalmology; at least, in regard to other branches, there are not as yet sufficient data *to enable us to* denominate physostigmine a general *remedy.* Physostigmine, or rather the preparation of

calabar-bean, has been employed in various nervous diseases, especially those which are viewed as dependent upon abnormal reflex irritability or as subject to such. Comparatively speaking, the use of the drug is most frequent in tetanus, and, indeed, a number of persons have testified to beneficial results, though many others assert that the remedy is inactive. A definitive decision on this question cannot at present be made; even a practical determination can hardly be expected in the immediate future, since chloral and bromide of potassium have lately pressed all other remedies for the treatment of tetanus into the background. Our experience in other spasmodic neuroses are as yet but very slight and inadequate; and the researches of Harnack and Witkowski convince us that we cannot with any degree of confidence venture to apply physostigmine to epilepsy.

In ophthalmology physostigmine has been tried as follows: First of all for removing atropine-mydriasis; but experience confirms the results of Rossbach's experiments, proving that it is of little value for this purpose. Far better results are afforded by its application to traumatic conditions of the eye, and to the cure of that organ from the paralysis of accommodation when it is among the sequælæ of diphtheria. Physostigmine is also used for rupturing posterior synechiæ, especially when the pupillary margin is too firmly attached by its periphery (here interchangeable with atropine); as also for anterior synechiæ. It has occasionally been used with satisfactory results by Laqueur, Weber, and others to diminish intra-ocular pressure, for instance in glaucoma, in which the employment of iridectomy is either impracticible or not attended with good consequences; as in staphyloma totale with greatly increased intra-ocular pressure. Recently physostigmine has been successfully employed by a number of persons for various affections of the cornea: keratitis superficialis and parenchymatosa, keratitis hypopion, with perforations and wounds of the cornea.

Dose and Preparations.—1. Physostigmine (eserine), not officinal, internally 0.0005 to 0.003; in ophthalmology.

2. *Faba calabarica*, not used.

3. *Extractum fab. Calabericæ*, in powders, pills, alcoholic solutions, and glycerites, 0.005 to 0.01 pro dosi (ad 0.002 pro dosi! ad 0.005 pro die!).

For instillation into the eye a solution of 0.2 extr. f. cal. : 10.0 gly-

cerine, or ½- to ¼-per-cent solution of the sulphate or muriate of physostigmine. Of the first, 2 to 4 drops; of the second, 4 to 8 drops to be used.

TREATMENT OF PHYSOSTIGMINE POISONING.

When the poisoning, as seen in previously mentioned cases, results almost solely from eating calabar-beans, the stomach must be at once emptied by emetics or the stomach-pump. The symptoms after absorption, namely, those of asphyxia and threatened cardiac failure, must be attacked according to generally accepted principles. Concerning the action of atropine, which may be regarded as a rational physiological antidote, no observations have yet been made.

Calabarin is a second alkaloid contained in the calabar-bean, which, according to Harnack, acts as a tetanic upon frogs, the reason being that the various extracts of calabar are distinguished from one another by their diverse effects on the spinal cord. Exact observations are, however, wanting.

PILOCARPINE AND FOLIA JABORANDI.

Jaborandi is the leaves and twiglets of a rustacea (pilocarpus pinnatus) that grows in South America. It was first introduced into practice by Cutinho.

From the so-called Pernambuco jaborandi Merk prepared an alkaloid as a salt, *pilocarpinum muriaticum*, in white, transparent crystals, of a slightly bitter, astringent taste, which dissolves colorless in an equal quantity of water. According to A. Weber, this is to be regarded as containing the active principle of the jaborandi leaves; 00.2 grm. of the alkaloid, he asserts, acts as powerfully as 5.0 grms. of folia jaborandi dissolved in 120.0 grms. of water.

PHYSIOLOGICAL EFFECTS.

After taking an infusion of jaborandi leaves, according to all that have made observations, nausea often arises, vomiting and a great weakness being the result, the latter lasting four to six hours, and following very soon upon taking jaborandi tea. This soon brought it into disrepute. Apparently this disagreeable accompaniment is the effect of an unknown ethereal oil.

As *pilocarpine* produces but a tithe of these unpleasant effects, and produces nausea only after the swallowing of too much saliva, but never causes vomiting and possesses valuable therapeutic properties (A. Weber), it deserves the preference for therapeutic applications.

According to Albertoni, the various kinds of jaborandi *leaves and pilocarpine* are of various efficacy.

In regard to the physiological effects of pilocarpine, we

gather our knowledge chiefly from the statements of A. Weber, Marmé, Lewin, and others.

The Eye.—If 0.001 grm. of solution of pilocarpine is dropped on the conjunctiva, the pupils begin to contract after ten minutes; after twenty to thirty minutes the maximum contraction is reached, which lasts three hours, when the pupils expand; after twenty-four hours they are in the normal state again. Albertoni experimented with a preparation which made the mydriasis last twenty hours after a myosis of two hours.

According to Tweedy, fifteen minutes after the application of pilocarpine it was followed by spasm of accommodation and reduced visual acuity, lasting ninety minutes.

Secretion of Saliva.—Five minutes after the subcutaneous injection of 0.0005 grm. of pilocarpine into the arm an increase in the secretion of saliva followed; the secretion is hastened as the dose is increased. According to Oehme and Lorisch, who experimented only with the leaves, man secretes, during two to three hours' time, 750 grms. of saliva for every 350 grms. of the drug injected. The larger the dose of pilocarpine, the larger is the amount of saliva secreted. Pilocarpine is of an acid reaction and acts well specifically. As a rule, the increase of the salivary secretion continues longer than that of the perspiration, lasting, on the average, one to two hours, occasionally, however, as long as eight.

Pilocarpine has this effect on the secretion of saliva by acting as an irritant on the peripheral fibres of the salivary gland (Carville); but there is also an irritation of the salivary centre in the medulla oblongata (Marmé).

Perspiration, which only very small doses (0.0005 grm.) do not provoke, begins a few minutes (in the average six) after the flow of saliva commences. It is first noticed on the head, and gradually spreads over the entire body. It is frequently attended by an intensely cold feeling, which causes the teeth of the patient to chatter. After a dose of 0.02 grm. (= 5.0 grms. folia jaborandi), perspiration will last one hour if the patient is out of bed, or two to three hours if he is in bed. In experiments on the paws of cats, pilocarpine has been shown to act not only by peripheral irritation of the sweat-cells (Lucksinger), but also by irritation of the sweat-centres in the spinal cord (Lucksinger, Naurowcki, Marmé). Very often patients show a reddening of the skin as one of the effects of the pilocarpine.

The *loss of weight* after a copious secretion of saliva and sweat lasting two or three hours amounts to an average of 2 kgrs., but may be as high as 4 kgrs. The loss through skin and lungs alone may be 350 to 930 grms. (Lewin). In consequence of this the tissue metamorphosis is greatly increased, as is evident at a thought.

Small doses of pilocarpine, according to Robin, Marmé, Lewin, etc., increase the following secretions: that of the ceruminous glands in cats; the tears, by exciting the peripheral as well as the central nervous apparatus; the secretions of the nasal mucous membrane, in most cases but slightly, however; the secretions of the bronchial mucous membrane, very copiously in powerful animals. Among weak animals there is not only no increase of the bronchial secretion, but there is none in perspiration.

The *secretion of milk* is, in general, but slightly increased, and doubtfully so; according to Röhrig, only indirectly through the more rapid circulation of the blood.

The *secretion and excretion of urine* are increased by small doses, yet to a limited extent, as with most of the other secretions. Larger doses do not interrupt the secretion; excretion becomes more difficult and even impeded.

The *secretions of the intestinal glands* are greatly increased by large doses, as is *peristaltic* motion. In consequence of this not only simple but soft and watery evacuations take place. However, Lewin and other physicians observed that the usual dose (0.01) produced no particularly noticeable changes in the functions of the human intestines; indeed, Lewin declares that there appeared to be more of a retardation of the natural function than the contrary.

According to Pelicier, an increase in the secretion of *gastric juice* occurs, but no change in that of bile takes place on dosing dogs with jaborandi. Lewin never noticed any effect upon the appetite in man; though quite often nausea and vomiting followed immediately upon the injection of pilocarpine, not as a consequence of too much saliva having been swallowed, but because of an irritation of the gastric branches of the vagus. In these cases appetite soon returned.

No important influence has yet been observed in the action of pilocarpine on *menstruation.*

All secretions increased by pilocarpine, even that of the *nasal mucous* membrane, may be checked by atropine.

Schmitz asserts that pilocarpine assists the growth of the hair.

Respiration is not affected by it.

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The disturbances in the cerebral and spinal action in animals under the influence of the drug are not perceived, owing to the predominating violent respiratory, circulatory, and abdominal disturbances. If these are counteracted by previously administered atropine, then, in the case of frogs, there will be paralysis of voluntary motion, while the reflex and respiratory centres do not appear to be affected.

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The *loss of weight* after a copious secretion of saliva and sweat lasting two or three hours amounts to an average of 2 kgrs., but may be as high as 4 kgrs. The loss through skin and lungs alone may be 350 to 930 grms. (Lewin). In consequence of this the tissue metamorphosis is greatly increased, as is evident at a thought.

Small doses of pilocarpine, according to Robin, Marmé, Lewin, etc., increase the following secretions: that of the ceruminous glands in cats; the tears, by exciting the peripheral as well as the central nervous apparatus; the secretions of the nasal mucous membrane, in most cases but slightly, however; the secretions of the bronchial mucous membrane, very copiously in powerful animals. Among weak animals there is not only no increase of the bronchial secretion, but there is none in perspiration.

The *secretion of milk* is, in general, but slightly increased, and doubtfully so; according to Röhrig, only indirectly through the more rapid circulation of the blood.

The *secretion and excretion of urine* are increased by small doses, yet to a limited extent, as with most of the other secretions. Larger doses do not interrupt the secretion; excretion becomes more difficult and even impeded.

The *secretions of the intestinal glands* are greatly increased by large doses, as is *peristaltic* motion. In consequence of this not only simple but soft and watery evacuations take place. However, Lewin and other physicians observed that the usual dose (0.01) produced no particularly noticeable changes in the functions of the human intestines; indeed, Lewin declares that there appeared to be more of a retardation of the natural function than the contrary.

According to Pelicier, an increase in the secretion of *gastric juice* occurs, but no change in that of bile takes place on dosing dogs with jaborandi. Lewin never noticed any effect upon the appetite in man; though quite often nausea and vomiting followed immediately upon the injection of pilocarpine, not as a consequence of too much saliva having been swallowed, but because of an irritation of the gastric branches of the vagus. In these cases appetite soon returned.

No important influence has yet been observed in the action of pilocarpine on *menstruation.*

All secretions increased by pilocarpine, even that of the *nasal mucous* membrane, may be checked by atropine.

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served with muscarine that after the period of contraction had passed a dilatation of the pupil followed.

With certain dosing a spasm of accommodation with dilated pupil can be stopped by a simultaneous introduction of atropine and muscarine; a somewhat larger quantity of atropine arrests the muscarine action on the eye and produces mydriasis and paralysis of the accommodation.

Respiration, as with physostigmine, is first accelerated, then retarded, and finally paralyzed.

In frogs with only 0.0001 grm. the *heart* stops in diastole, and this state may last half an hour. If the heart is irritated, one or more strong systoles will always follow. Schmiedeberg and Koppe assume that this is a consequence of an irritable state of the checking apparatus. The pulsations in men and dogs first become more rapid, but afterwards decline. The cause of the increased frequency is unknown; the later decline is also referred to irritability of the checking system.

The *blood-pressure* first declines, but increases afterward. The peripheral vessels are dilated.

The *digestive organs* are affected, as in the case of physostigmine; there is a flow of saliva; the cause of the vomiting and the diarrhœa is as in the latter tetanus of the intestine. There is an increased secretion of bile and pancreatic juice (Prévost). The secretion of the tear-glands, of the bronchial mucous glands, and also that of urine is increased.

Death from muscarine poisoning ensues finally either from paralysis of the heart or of the respiratory organs.

The action of muscarine on the eye, heart, intestines, salivary glands, etc., is arrested by atropine. The reverse does not obtain.

THERAPEUTIC APPLICATION.

Muscarine has not been utilized therapeutically; at least there is no need for it in practical ophthalmology (according to Krenchel), as physostigmine renders better service for the same indications. Donders believes that it might perhaps be employed for defining the incurvation of the lens in contracted state of the ciliary muscle and dilated pupil.

The dosing must be established from the physiological *experiments.*

Treatment of Muscarine Poisoning.—Cases of poisoning

happen very often, not from pure muscarine, but from the fungus containing it. The first thing to be done, presuming that severe vomiting and diarrhœa have not spontaneously occurred, is to empty the stomach by emetics and the stomach-pump, while the intestines must be cleared by oily purgatives. If the symptoms caused by absorption appear, then the physiological antidote, atropine, must be given hypodermically in doses carefully calculated from the experiments made on animals. A symptomatic treatment would afterwards be requisite according to the indications in each case.

The Alkaloid of Tobacco.

NICOTINE.

Nicotine, $N_{16}H_{14}N_2$, a non-oxygenous double acid vegetable base, is at first colorless, but becomes afterward, owing to partial decomposition, a brownish liquid having an alkaline reaction and an intoxicating tobacco odor. It, as well as its salt, is easily soluble in water. It is one of the most active elements of the leaves and seeds of various kinds of tobacco (Nicotiana tabacum, rustica, macrophylla). Least nicotine (2 per cent) is found in the more palatable and therefore "finer" tobaccos, as the Havana. In the poor kinds from 4 to 8 per cent are found, but these estimates are probably exaggerated.

PHYSIOLOGICAL EFFECTS.

Nicotine is one of the strongest poisons, and approaches very closely to prussic acid as regards the small doses which are sufficient to kill men and animals. Small living creatures, as birds, die from inhaling inappreciably small quantities that are evaporated from a drop held before the bill. Rabbits, cats, and dogs succumb to 0.005 grm., and men probably from scarcely greater quantities, as 0.003 grm. have produced serious symptoms of poisoning.

It is closely allied to the physostigmine group as regards the quality of its action.

Reception and Changes of Nicotine in the System.—Nicotine is absorbed through the unbroken skin (Roehrig); very rapidly through all the mucous membranes, so that fatal doses may cause death in from 20 to 30 seconds after reception.

It is not decomposed in the body, but found again as such in all the organs (stomach, intestines, blood, liver, spleen, kidneys and brain) and in all the secretions (urine, saliva) (Dragendorff). It is also said to retard the decomposition of animals *poisoned* with it (Melsens).

General Symptoms. Restlessness is exhibited in frogs when the quantities are not too large; sometimes there is a cry of pain, which is soon followed by violent excitement, and an unconscious state succeeds after a little, during which severe clonic spasms occur then immobility, and afterward a highly characteristic condition of the feet (the fore feet pressed together as if in supplication or laid tightly along the body, the upper part of leg at a right angle to the longitudinal axis, the lower part of leg completely bent. In this period, in which the head is drawn in as if "ducked," the pupils and the nictatory membranes no longer act on being irritated, and the voluntary movements and respiration stopped, is succeeded by fluttering muscular contractions, great diminution of reflex excitability on irritating the skin, then relaxation of the entire muscular system and general paralysis. The heart usually pulsates for some time after death.

In small warm-blooded animals, as birds, death ensues in a few moments, even with relatively small doses, owing to general paralysis. With somewhat smaller quantities there follow weakness, fluttering of the wings, tetanic stiffness of the legs, difficulty of respiration, and death.

Larger warm-blooded animals—dogs, cats, etc.—fall down paralyzed without any spasms, and die in 20 to 30 seconds after taking large fatal doses. When large but not immediately fatal doses are given, they first utter cries of pain, but soon become unconscious, and then fall into severe convulsions in which tonic and clonic spasms alternately are continually repeated at short intervals until death ensues, either by suffocation from respiratory tetanus or from general paralysis. Even small and non-fatal doses will cause spasms, followed by excessive debility, so that the animals cannot stand up, and recovery to health is very slow.

Even small doses of 0.001 to 0.003 grm. of nicotine have very toxic and lasting effects on men. Dworzak and Heinrich (under Schroff's direction) describe the symptoms as follows: First a burning sensation on the tongue; itching in the throat and flow of saliva; then headache, giddiness, drowsiness, indistinctness of sight and hearing; extraordinary sensation of weakness and fainting-fits; difficult and impeded respiration; pallor of countenance; distorted features; icy coldness of hands and feet; nausea; vomiting; eructations; violent desire to stool; trembling of the extremities and shaking of the whole body; clonic spasms, es-

pecially of the respiratory muscles, in consequence of which the breathing becomes difficult and impeded, every respiration consisting of short gusts in rapid succession, so that the air can only enter and escape from the lungs by fits and starts. This terrible condition lasted three full days and almost drove the daring experimenters to despair. Very large fatal doses act in an exactly similar manner as in the case of other warm-blooded animals.

Exceedingly small and harmless doses seem to increase the mental and physical powers and the reflex excitabilities; to lessen the appetite and stimulate the movements of the intestines. When small doses are begun with, the organism of animals also (rabbits, Anrep) can be accustomed to continually increasing ones. If, on the other hand, a large dose is given at once to frogs and rabbits, these will be affected quite differently during several days by repeated poisonings than are normal and non-poisoned animals, although they appear to fully recover after the first poisoning, and not to differ in any respect from normal animals; yet after a second dose of the same size some symptoms of poisoning appear that are always present in a first case; for instance, the fluttering muscular contractions and the spasms do not appear, but the stoppage of respiration, the loss of voluntary motion, and the general paralysis do. The second dose has, moreover, a greater effect on the heart in the case of frogs and on the respiratory centre in warm-blooded animals. The cause of this action is doubtlessly due to the fact that, despite the normal appearance of the animals, the organs more immediately affected by the nicotine have not yet quite recovered their normal condition, and that the heart of the frogs and the respiratory centre of the rabbits have remained in a debilitated state, and that an additional dose increases the still present weakness; that the spasmodic centre has also been weakened by the first dose, and that a second dose is no longer strong enough to excite it. If the second dose is three or four times larger than the first, spasms will again take place, but are not so strong as the first time (Anrep).

Action of Nicotine on Individual Organs.—From the foregoing observations it would seem that the action of nicotine, like that of the other alkaloids, is directly applied to the nerve-substance; at all events, the disturbances cannot be traced to changes in the blood. The dark red color of the blood is solely attributable to respiratory disturbances.

If the blood-corpuscle is quickly decomposed when nicotine is directly mixed with the blood, this must be solely attributed to the strong alkalinity of the poison.

Brain.—That nicotine in very small doses facilitates the mental processes, disposes to intellectual work, and dispels the desire to sleep may be easily inferred from the effects of tobacco, although we have no direct evidence from infinitesimal doses of pure nicotine. In somewhat larger doses both warm- and cold-blooded animals present in the beginning evident symptoms of excitability of the cerebral functions, which, however, are soon succeeded by contrary indications, brain-paralysis and unconsciousness.

Spinal Cord.—Freusberg justly maintains that small doses at first excite all parts of the spinal cord, and also more particularly the reflex communicating apparatus (contrary to the opinions of Rosenthal and Heubel). It must not be concluded from this, however, that when a frog is in tetanus it will not react any longer under irritation. The experiments of Freusberg on decapitated and dying frogs are especially interesting and important in this connection. After they had lost all reflex action, twenty-four hours after decapitation, and only showed reaction by shutting the lids on irritation to the cornea, they could be so reanimated by injection of nicotine that an hour afterward an irritation to the skin was promptly answered by marked reflex motions. This reanimation of the spinal cord lasted from one to three days; when irritations were made at short intervals, it soon grew weaker, but recovered after a short time. The bodies of the nicotinized frogs preserved a natural appearance for a remarkably long time, and very light, medley-colored frogs acquired a dark shining skin. According to Anrep, the fluttering muscular contractions which are always observed in frogs when poisoned by nicotine are owing to a predominant central origin.

This excitability of the spinal cord increases to tonic and clonic spasms which continue or arise (according to circumstances) in the same peculiar way after decapitation (Freusberg), and which cannot be stopped by artificial respiration. This last fact, and its existence in cold-blooded animals, shows us that they are independent of circulatory disturbances (Uspensky).

This excitability is followed, more rapidly than in strych-

nine poisoning, by an insensibility of the spinal cord to direct and reflex irritation and by total paralysis.

The deportment of the peripheral nerves has been more minutely examined in cold-blooded animals. The intramuscular terminations of the motor nerves are first excited (hence the weak fluttering muscular contractions after separation from the spinal marrow), then paralyzed, while their roots long retain electro-motor qualities (Rosenthal). The contraction of the pupils which is always observed in nicotine cases seems to be caused by irritation of the motor oculi. The sensitive nerves are affected sooner, much more strongly, and for a longer time than the motor nerves (Anrep).

Direct muscular irritability is maintained for a long time. The fore-feet of frogs always sink into a cataleptic state, and become stiff and wax-like for 20 to 45 minutes; they afterward assume any desired position and maintain it until changed, and all this owing to a change in the muscular substance itself (Anrep).

The respiration is excited at first, and becomes more frequent, panting, and hissing until there are tetanic inspiratory spasms and spasms of the glottis, even after the cervical *vagi* have been divided. It is finally retarded and paralyzed, very likely by the irritation and paralysis of the respiratory centre in the medulla oblongata.

The *circulatory organs* are affected in the following way: The heart of the frog pulsates slower and slower after small doses (0.0001 gramme), and stops at length in diastole, owing to irritation of the contractile apparatus; after some time a second period follows, in which the contractile system is paralyzed, so that the heart begins to beat again regularly but somewhat more weakly. This second effect is therefore similar to that of atropine, with the single difference that with nicotine sinus-irritation is produced later; muscarine effects a stoppage of the heart-action, which is no longer possible in atropine poisoning. Truhart and Schmiedeberg conclude from this that the parts attacked by nicotine and atropine in the contractile apparatus cannot be the same, and assume that nicotine exerts its paralyzing action only over a hypothetical connecting part lying in the heart between the root of the vagus and the contractile nerve-centres proper, while atropine paralyzes the real contractile centres.

In warm-blooded animals the action of the heart is first

retarded in consequence of the vagus irritation; then, when the vagi have been paralyzed, it is again accelerated, but then again retarded for the third and last time, when the excitability of the heart motor apparatus is lessened. The blood-pressure declines as long as the vagus excitement lasts, when it immediately rises, to sink again. The primary contraction and the later dilatation of the blood-vessels depend partly on the relative changes in the vaso-motor centre (Uspensky), and partly on the influence of the peripheric vascular nerves themselves (see Basch and Oser).

The surface temperature falls, and only incidentally rises during the spasms.

The Digestive Organs.—Small doses increase the secretion of saliva by reflex action, and diminish the sensation of hunger, and strengthen and accelerate the movements of the bowels. If a minimum quantity be injected into the jugular vein, the intestines, from the stomach to the rectum, will be contracted, and especially the small intestine, to the entire or almost entire disappearance of their lumen. The intestinal gases and excrementitious matters are thrown rapidly towards the anus, and a kind of tetanus of the colon sets in that is not lessened either by dividing the vagus nor compressing the abdominal aorta, and in which the tri-splanchnic nerve cannot exert its contractile influence (Nasse). Coincidentally with this tetanus the intestines become pale. Then follows a period of rest, during which the vessels refill, and finally another violent peristaltic action occurs. The larger the dose the more rapid and intense will be this effect (Nasse, Basch and Oser). The intestinal tetanus is induced by violent excitement of the intestinal ganglia, the severe peristaltic motion by the irritation of an intestino-motor centre situated in the medullary substance, as it appears after the aorta has been ligated and the poison injected only through the carotid to the brain and spinal cord (Basch).

The bladder and the womb are also said to show contractions (Nasse).

Nicotine itself is not used in medicine.

TOBACCO.

The use of tobacco as a means of giving enjoyment in the various ways of smoking, snuffing, and chewing has spread almost over the whole world since 1560; a fact which would

be impossible from a mere spirit of imitation, but is rather to be referred to its physiological effects.

The principal effect of tobacco, whether in the form of snuff, chewing or smoking tobacco, must be certainly attributed to the volatile nicotine in the tobacco-leaves, and which we have just discussed at such length.

Still, perhaps, we must also take into account nicotianine, $C_{22}H_{32}N_2O_3$, an indifferent, bitter, and very volatile matter with a tobacco odor, and which when given in its purity causes sneezing, headache, nausea, and vomiting, but which is probably nothing but a combination of nicotine with a volatile acid (Hermbstädt, Landerer, Buchner). A large series of very active matters which are developed only in preparing the tobacco, burning cigars for instance, must also be taken into account.

The presence of nicotine in tobacco-smoke has been denied by Vohl and Eulenberg, but maintained by Heubel on the strength of more recent experiments. Pure nicotine is certainly decomposed at moderate temperatures, as in the simple process of steaming for drying; still the nicotine is actually present in tobacco-leaves as a stable salt, and it loses but little of its effectiveness by heat. However this may be, a quantity of volatile bases are developed during the smoking of tobacco, and all of them, with the exception of ammonia, are pyridine bases—viz.: pyridine, C_5H_5N; picoline, C_6H_7N; lutidine, C_7H_9N; collidine, $C_8H_{11}N$,—all of which, according to Vohl and Eulenberg, are similar to nicotine, but weaker, and, like it, cause contraction of the pupil, spasms, etc. Besides hydrothionic acid, carbonic-acid gas, marsh gas, cyanic hydrogen, along with nitrogen and oxygen, have been found in tobacco-smoke in small and very variable quantities. The fact that very strong tobacco can be used for cigars which could scarcely be smoked in a pipe is explained by the presence of the highly volatile and narcotic pyridine in less complete combustion processes as in smoking a pipe, while in the combustion of good cigars with white ashes but little pyridine and more of the less active collidine are developed.

The physiological effects of smoking are dependent, therefore, on the above-mentioned ingredients of the smoke, and the juices that are absorbed when holding a cigar in the mouth, and which, of course, like the residue in the pipe, is far richer in nicotine and far more poisonous than the smoke.

The first attempts at smoking generally produce rather serious toxic symptons, which are exactly the same as have been described by Dworzak and Heinrich of their personal experiments with nicotine. Soon, however, a person gradually becomes more habituated to it, and then those pleasant and useful symptoms appear which so rapidly introduced and popularized this pleasure among mankind —a comfortable feeling of mind and greater zest and endurance for mental and physical labor. Especially with habitual smokers it is found that refraining from the indulgence disturbs the general tone of the system and diminishes their capacity for work. In the German army in active service the soldiers are very properly furnished with ample supplies of smoking-tobacco, because it has been observed that smoking enables men to endure severer fatigue upon smaller nutrition and with greater alacrity and cheerfulness. These results are to be attributed to the action of nicotine in very small quantities upon the brain and spinal cord.

The habit, long continued, permits the use of large quantities; but in this direction there is a limit, and when this is passed the result is diminution of appetite, catarrh of the stomach, chronic catarrh of the throat and larynx, chronic conjunctivitis, and more rarely palpitation of the heart and *delirium cordis*, trembling of the limbs, hypochondria, and irritability. Hirschberg asserts that a kind of amblyopia is sometimes produced by tobacco; it takes the form of a specific, double disturbance of vision, a sharply defined paracentric scotoma, which covers the fixation-point, and thence spreads in an oval shape, which extends beyond Mariotte's spot; the scotoma for white is only a comparative, never an absolute; acuity of vision is reduced one third to one thirtieth of the normal; amaurosis never occurs; the appearance of the pupil is at first normal, afterward the maculous half is slightly discolored.

Few instances of death from smoking are known: a young man died after smoking his first two pipes; two young men, æt 17 and 18 respectively, died after uninterrupted smoking.

Snuff according to Schlösing contains 2 per cent, according to Vohl and Eulenberg only 0.03 to 0.06 per cent; the variations are to be explained by the difference in the preparation and adulterations. From the usual manner of *putting snuff into* the nose generally local action only is pro-

duced: increased secretion of mucus, violent sneezing, dulness of smell, and, inasmuch as snuff always enters the throat, œsophagus, and stomach, occasional catarrh thereof. Certainly if it entered directly into the stomach in considerable quantity, the symptoms of nicotine poisoning would obtain; in point of fact, death has been known to occur after the administration of 2 to 4 grms. in this manner.

The effects of chewing tobacco vary, whether the tobacco-leaves themselves, a cigar for instance, or whether what is called chewing-tobacco is used. In the first instance serious symptoms result; the nicotine has been known to cause death after chewing half a cigar. Chewing-tobacco, so called, is rendered much less dangerous by the mode of preparation and by the admixture of foreign innocuous vegetable matter; it chiefly tends to produce buccal and gastric catarrhs. We are unable to say whether the irresolution and want of mental clearness noticed in many tobacco-chewers is the effect of the habit or not.

Dietetic and Medicinal Uses of Tobacco.—We have stated above the action of tobacco upon the nervous system which has caused it to be generally adopted as a means of indulgence. It is needless to say that it may be dispensed with; nor will we waste any words arguing with the opponents of tobacco about the æsthetics of chewing, snuffing, or even smoking. All that we insist upon is that every-day experience demonstrates that moderate quantities may be indulged in without injury; for with moderate use the symptoms of chronic poisoning present only in exceptional cases where there is some individual idiosyncrasy; otherwise such symptoms manifest themselves only in cases of excessive indulgence.

The conditions which forbid the use of tobacco now require consideration. Among them come, first of all, cases of acute and chronic catarrhal and inflammatory affections of the mouth and throat, and also, in our judgment, cases in which there is a tendency to dyspepsia and gastric catarrh. Next, smoking must be avoided in cases of conjunctivitis and other ocular inflammation, inasmuch, especially if it is carried on within a closed room, it may even cause catarrh of the conjunctiva tunica. The question of the relation of smoking to affections of the lungs has been very much discussed. In our opinion catarrh is caused by it only in exceptional cases, and indirectly when chronic

pharyngeal catarrh extends downward. Nevertheless, in all cases where the organs of respiration are affected, smoking must be prohibited, and for the peremptory reason that in all such cases provision must be made first of all, and under all circumstances, for a supply of good, pure air. Persons who have heart-disease must forthwith abandon the use of tobacco when they show any signs of palpitation—which, however, are not always manifested. We cannot here give a general opinion in regard to neuropathic cases.

The *therapeutic* value of tobacco is insignificant, and its use as such may be safely dispensed with.

Formerly it was most frequently used in cases of intussusception; at the present day tobacco injections have been pretty generally abandoned, for the reason that the result is uncertain, and because of the attendant danger of poisoning, which is apt to set in. It has been recommended also in cases of chronic constipation (without exact specification of varieties); as a matter of fact, with many persons smoking in the morning is followed by a regular stool—in any other form it would hardly be prescribed for constipation. Confirmation is wanting of the value of tobacco in cases of spasm of the glottis, *asthma bronchiale*, whooping-cough; the same is true with regard to nervous *singultus*.

Dose, *folia nicotianæ*, internally, infusion, 0.02 to 0.15 pro dosi; in clysmata, tobacco smoke has been used or an infusion of 0.5 to 1.0: 120 to 200.

Treatment of Nicotine Poisoning.—When acute poisoning has been produced in the stomach, it must be emptied, best by the stomach pump; administering tannin may also be recommended. Symptoms caused by absorption call for symptomatic treatment, directed towards the collapse, respiratory disturbances, etc.

For the treatment of all diseased conditions resulting from chronic indulgence in tobacco, the first requisite is abstinence from the use of tobacco; and, as a rule, this proves a sufficient remedial measure. Where the derangements still continue, they must be treated in accordance with the special pathological conditions that prevail.

Indian tobacco, of *Herba lobeliæ inflatæ* (*Lobeliaceæ*), does not call for any special notice here, on account of our utter ignorance of its active principle, and on account of its very questionable utility. Moreover it is extremely noxious.

At the present day recommendation of lobelia is limited to its application in pulmonary affections, as an expectorant, and as a presumed successful remedy in so called "asthmatic attacks" and "spasmodic" coughs. English and American, and some German physicians likewise report having found it of decided benefit as a palliative in all forms of dyspnœa and annoying cough, when they were of a "nervous" character, and not produced by anatomical disturbances of the respiratory apparatus. Even when these manifestations present in a secondary form depend-

ent upon other conditions (heart disease, bronchial catarrh, etc.), lobelia is said to have mitigated the violence of attacks of coughing and the strong feeling of oppression. Other observers have not been able to confirm this result; at any rate, it is certain that no positive and sure benefit is to be expected.

Dosage and Preparations.—1. *Herba lobeliæ*, 0.05 to 0.15 *pro dosi* (2.0 *pro die*) in powder, infusion, and decoction. 2. *Tinctura lobeliæ*, 5.30 drops *pro dosi* (0.3 to 1.5).

ALKALOIDS OF CURARE, CONIUM, CYNOGLOSSUM, AND THE ALKYDERIVATIVES OF VARIOUS ALKALOIDS.

The alkaloids hereinafter named and the alkyderivates of many other alkaloids exert a similar action upon the animal organism, and are particularly characterized by paralysis of the muscular terminations of the motor nerves, extending to the smallest fibres, together with sustained irritability in the substance of the muscle itself. They are *curarine*, the curare arrow-poison, an alkaloid obtained from various species of strychnine and coculus; *coniine* and *conydrine* ($C_8H_{17}NO$) obtained from hemlock; the as yet unknown constituents of several kinds of borage, of cynoglossum officinale (cynoglossine), anchusa officinalis and echium vulgare; a partial product of narcotine, colarnine ($C_{12}H_{13}NO_3+H_2O$), and, besides, the quite remarkable alkyderivatives of numerous alkaloids, that is to say, alkaloids in which H is represented by a radical ethyl, methyl, amyl; methyl-delphinine, methyl-strychnine, -brucine, -atropine, -chinidine, -chinine, -cinchonine, -veratrine, -nicotine, ethyl-strychine, -brucine, -nicotine, -amylcinchonine, -veratrine; finally the ammonium bases of simple carburetted hydrogen, for example, tetramethylammonium iodide. Hermann and V. Meyer have also found in many kinds of beer an active constituent of a curare nature, without having been able to ascertain from which particular one of the vegetable substances used in the preparation of the beer it was derived.

Of all these, the operation of *curarine*, as above indicated, is the most potent and in the smallest quantity (0.000005 of a gramme), and we, therefore, shall examine it with the closest attention. In addition to curarine, therapeutic application has been made of coniine, but only to a small extent.

CURARINE AND CURARE.

By the name of curare (worara, urari) are known certain kinds of arrow-poison, obtained by the indigenous races of South America, from

various species of strychnos, cocculus and paullinia (?). These substances come to the market either in shells (calebashes) or in earthen pots (curare-pots) and appear in the form of impure brown resinous lumps, which vary greatly in the strength of their active principles. Curarine, which was first exhibited by Von Preyer, was denoted by the formula, $C_{18}H_{21}N$ by Th. Sachs. The article of commerce known by the name curarine is frequently an impure preparation, and, indeed, in some cases an entirely different substance; for example, phosphate of lime.

PHYSIOLOGICAL ACTION.

Curare produces about the same poisonous effect upon frogs and warm-blooded animals, whether it is injected hypodermically or directly into the blood. Very large quantities are not needed in order to accomplish the same results, through introduction into the stomach. The reason why small quantities do not act with as much poisonous efficiency through the stomach, is that such small quantity of curare immediately after absorption into the blood is ejected through the kidneys, and that the necessary amount of poisonous matter, cannot exert its full action by means of a more gradual absorption by the mucous membranes; a ligature of the renal arteries is followed by rapid poisoning, even when the curare is introduced into the stomach (Bernard, Hermann). Why the action of the poison, when introduced by subcutaneous injections, should continue a long time, notwithstanding the fact that the curare is speedily eliminated, is not known. Hermann's explanation of the phenomenon is that when a change has once been wrought upon the extremities of the nerves, considerable time is required for their restoration, even long after the poison has been ejected from the body; positive proof of this complete separation is, however, as yet wanting, so that we might, with equal reason, assume that when the curare has once been been assimilated with the substance of the nerve extremities, it but gradually frees itself from this connection.

The lower the animal in the order of creation, the more slowly does curare produce its effect upon the motor nerves; in fishes, the first action of curare is to paralyze the central organs of voluntary motion and respiration; reflex motions take place long after this paralysis has been produced, and it is not until after a considerable period that the motor nerve extremities are paralyzed. Fishes which are able to survive removed from water—for example,

eels—are not affected by curare, out of water, more powerfully than if the injection had been introduced into them in the water; it follows, that the difference between the curare's action upon fishes and other animals which live out of the water, does not result entirely from the rapid ejection of the poison through gills immersed in water. In electric eels, paralysis of the electric nerves occurs subsequently to that of the motor nerves. In snails, star-fish, holothuriæ, a paralysis of the central organ of voluntary motion takes place, but not of the motor nerve extremities; inasmuch as the last-named species have no striped, but smooth muscles only, the principle would seem to result, that curare with animals of the higher as well as of the lower orders, attacks chiefly the nerves pervading the striped muscles (Steiner). In frogs, likewise, direct injection into the blood produces paralysis of the central organ of voluntary motion at first, and with extraordinary rapidity, long before paralysis of the motor nerve extremities occurs (Kölliker).

Absorption and Ejection.—As has been already stated, the absorption of curare by the mucous membrane takes place so slowly that the curare may be sucked out of a wound without danger, and poisoning can be produced only by the use of enormous quantities. Hence the supposition that prevailed for a long time that curare, used internally, was not a poison at all. Elimination is effected through the urine; hence, other animals can be inoculated with curare by means of the urine of animals impregnated with it.

We will describe only the phenomena in frogs and warm-blooded animals; we have already stated its influence upon the lower animals.

Von Preyer and others observed in men, after the introduction of small quantities of curare (0.01 to 0.05 grammes), rush of blood to the head, violent headache of short duration, weariness, and torpor of movements, and marked increase in the salivary, tear, sweat, urine, and nasal mucus secretions, saccharine urine, violence and acceleration of pulse, quickened respiration, rise of the body temperature. With larger quantities (0.1 gramme), in men, Voisin and Lionville observed ague, increase of the weaker heart pulses, rise of temperature, paralysis of the lower extremities, violent headache with entire preservation of consciousness and sensation.

Shortly after hypodermic injection, frogs and warm-

blooded animals sink as if exhausted upon the ground, then for a considerable time make vain efforts to raise themselves, finally remain lying motionless and breathless and, then, cannot be forced to make any movement, either voluntary or muscular, by the most acute pain. Upon this, in consequence of the paralysis of respiration, carbonic acid accumulates in the blood, and this carbonic acid and not the curare at last paralyzes the heart and puts an end to life. Frogs, on the other hand, which are able to absorb enough oxygen through the skin, without respiration or the use of the lungs, maintain their heart pulse for days, and can in the end gradually entirely recover without any artificial assistance.

Action upon the Organs and Functions of Frogs and Warm-Blooded Animals. — It is the ends of the motor nerves in the striped muscles upon which the curare's action is exerted, first, as soon as an extremely small quantity has been introduced, and it is upon these that the action is most important. The ends of these motor nerves are entirely paralyzed, while, at the same time, both the trunks of the motor nerves and the central organ in the spinal marrow, and likewise the substance of the striped muscles themselves remain sensitive; this fact, which is of the greatest importance in the theory of muscular sensibility, was first recognized by Kölliker and, afterward, by Bernard and Funke, and has been established by a long succession of experiments. If, in a frog, a ligature is placed upon the extremity of an artery and poison is injected into the trunk, the extremity from which the current of blood has been shut off remains, both voluntarily and reflexly, at least until the curare has permeated by diffusion into the extremity cut off from the supply of blood. That, however, it is the extremities of the motor nerve endings, and not the nerve trunk itself, which is paralyzed is shown by the fact that in the extremities the electro-motor action is not only not weakened but even strengthened (Funke, Röber); and, also, by the further fact that the appropriate muscle can be set in motion by a piece of nerve which has been dipped in a solution of curare, afterward as well as before. Hence it results, as the muscle itself remains directly sensitive (see below), that the sole points vulnerable to curare are the extreme termination of the motor nerves in the muscle cells. Upon administration of the poison in the ordinary quantity, sufficient to totally paralyze the motor nerve ter-

minations, the sensitive nerves, the spinal cord and brain experience no injury. This is shown from the fact that upon perceptible irritation of the skin over parts of the body that have been poisoned, reflex motions take place of a leg which had not been poisoned and from which the circulation of the blood had been shut off, and from the fact that the leg can also be moved voluntarily; nothing of which could take place, if the sensitive nerve terminals, or the means of transmission to and from the brain, the motor and reflex central organs had been paralyzed. Hence, it must be assumed as highly probable that either cold-blooded or warm-blooded animals, impregnated with curare (the warm-blooded, when supplied with air by artificial means), may retain full sensitiveness, at least for a certain period, to all impressions produced upon their bodies. We certainly are obliged to agree with von Bezold and Lange, whose experiments upon frogs we have repeated, when they say that the sensory apparatus in the spinal cord which causes reflex motion, also, undergoes a change, inasmuch as the reflex motion at first even quickens and soon becomes tetanic, then diminishes, and finally ceases altogether. In the cutaneous terminations of the sensory nerves Lange likewise thinks that he can show that finally there is a diminution of irritability. We, however, consider the proofs assigned as insufficient.

The striped muscles remain sensitive, as already stated, though, it is true, those in cold-blooded animals remain somewhat less sensitive to faradic irritation than the muscles into which the poison has not been introduced (G. Rosenthal), but this fact is not to be construed to the prejudice of the muscle into which curare has been introduced; for the potency of the latter is not only not diminished (Kölliker and Pelikan), but exhaustion from a long series of efforts ensues even at a slower rate; recovery follows more quickly and better than in normal muscles (Funke); and in warm-blooded animals also very small quantities of curare produce an increase and acceleration of the successive convulsive movements of the muscles (Rossbach). Whether this results from a more copious flow of blood into the muscle affected by curare (Röber) or from a direct exciting action by curare upon the muscular apparatus in question, which it in the end paralyzes, is doubtful. The restriction of the action of very small quantities of curare to the motor nerve terminals, and the exclusion of other important organs

from this action, explains in the simplest manner why the voluntary respiratory and reflex movements of the body entirely cease, while the heart pulse and the vascular nervous system are uninjured (vascular reflexes taking place in the lower degrees of poisoning), and why cold-blooded animals come back to life of themselves, and warm-blooded animals may be kept alive provided respiration is artificially maintained.

Paralysis of the vaso-motor nerve endings in the vessels and a dilatation of the blood-vessels does not take place until far larger quantities have been administered than is necessary for paralysis of the muscle nerves (Bidder); it is true that in the end these vessels are likewise paralyzed, the blood pressure subsides and even direct irritation of the vascular nerves has no longer restrictive power; at about the same time *sympathetic* irritation is no longer followed by an enlargement of the pupil (Kölliker).

No safe explanation has yet been found for the increase of all secretions and for the sugar in the urine (particularly in warm-blooded animals which may be kept alive by artificial respiration). In the absence of conclusive experiments, it is conjectured that the result is produced by the paralysis of the vessels, occasioned by the excessive blood supply of the secretory organs in question, and the salivary secretion, also, by the paralysis of the secretory glands.

For a long time the heart itself is little affected; the vagus terminals only, are paralyzed (and this by no means uniformly) so that acceleration of the pulse occurs; irritation to the vagus no longer produces a retardation of the heart beat, only now and then still stronger acceleration, because the accelerating vagus cells are not paralyzed (Wundt, Böhm). It is only after the use of very large quantities that the force of the heart-beats diminishes somewhat; the heart is always the organ which survives the longest.

Peristaltic motions are accelerated and strengthened, after using curare, by the paralysis of the trisplanchnic nerve, in a similar manner as with the heart. (See above.)

On taking small quantities the *temperature* steadily rises (in human beings), for reasons which have not yet been discovered; after longer action of the curare it invariably falls, and probably for the reason that tissue metamorphosis is arrested by curare to a great degree. *According to Röhrig* and Zuntz the absorption of oxygen and the

release of carbonic acid subsides to a small fraction of the normal amount, and that too while the circulation is unaffected. From this, these authorities assume that the suspension of activity of the nerves of the striped muscles must be regarded as the cause of this remarkable falling off; the larger part of the process of oxidation which takes place in the muscles is produced wholly by this innervation and must necessarily be brought to a stand by the curare: moreover, curare reduces to a minimum the heat adjustment, which is probably primarily induced by an incessant faint reflex excitement of the motor nerves which increases with the difference between the temperature of the animal organism and of that by which it is surrounded.

In warm-blooded animals *death from curare* results from paralysis of respiration and is mere suffocation; the convulsions which occur shortly before death indicate a gradual revival of the sensitiveness of the motor nerve terminals, and in consequence of them the irritation produced upon the spinal cord by the carbonic acid may again cause muscular spasms (suffocative convulsions).

THERAPEUTIC APPLICATION.

The use of curare for medical purposes is very limited, despite the extent to which its physiological effects have been investigated. It is recommended mostly for traumatic and rheumatic tetanus; but the results hitherto attained do not encourage more experiments. It is also recommended (from experiments made on animals and in some cases on human beings) for toxic strychnine-tetanus. (See treatment of poisoning by strychnine).

If the recent communication of Offenberg, who cured a case of thoroughly developed *lyssa humana* (up to then considered incurable) with curare, were confirmed by further experience, the drug would gain great importance. As the case is related, we cannot doubt the accuracy of the diagnosis. His doses are remarkable. He injected 0.19 curare in 7 injections during 4 hours, using a 5 per cent solution and, when convulsions threatened to reappear after 30 hours, he injected 0.03 curare.

Dose.—Curare is used endermically. Ten drops of a 1 per cent solution, or in subcutaneous injections beginning with 0.03 to 0.005 pro dosi.

Curarine has barely been tried.

Treatment of Poisoning by Curare.—This poisoning is not likely to be observed except in a physiological laboratory. If the poison is introduced into the stomach, an emetic should be given. If curare penetrates a wounded skin, a ligature should be applied and unbound occasionally so that only small doses may be absorbed. If asphyxia threatens, artificial respiration must be instituted to save life.

Coniine, $C_8H_{15}N$, the fluid, poisonous deoxidized alkaloid of conium (Hb. conii maculati s. cicutæ) from conium maculatum (umbelliferæ).

Physiological Effect.—Coniine is of a repugnant odor and of an irritant taste. It paralyzes the motor terminal filaments of the nerves (like curare), and leaves muscle irritable (Kölliker); later on the motor centres in the brain and the spinal cord are paralyzed (Damourette). In consequence of this paralysis, which also attacks respiration, we see asphyxia in cold-blooded animals and convulsions in warm-blooded animals, which convulsions, according to Guttmann, are not due only to poisoning with carbonic acid. The heart, the vagus terminals which are paralyzed (Böhm), survives the other organs. Coniine paralyzes the sensory nerve terminals, therefore ointments containing it cause insensibility.

Thus the physiological effects of coniine range between nicotine and curarine.

The treatment of poisoning by coniine is the same as that of curare; artificial respiration saves the life.

Doses and Preparations.—Formerly conium was alternately recommended and condemned; now it is almost obsolete, and seems destined to remain so, despite the recent warm recommendations for its employment (as by Murawjew). And this is proper, as unprejudiced observation shows that conium offers no advantage over other remedies which have a milder effect. It also decomposes easily and the dry plant is entirely useless. We may, therefore, ignore its use for divers diseases, with the exception of scrophulous ophthalmia, for which it was formerly much praised and is yet used. Formerly preparations of conium were employed in all forms of erethic scrophulosis; now it is used in ophthalmic affections only, both internally and externally. It is also used occasionally in neuralgias (Nega, Murawjew), but according to W. Reil's experiments it must then be avoided in anæmic people. For pertussis it benefits even less than atropia.

Administered *externally*, conium sometimes relieves pain. It has been used for this purpose in neuralgia and also in tumors (cancer) with some effect.

Doses and Preparations.—1. *Coniinum* internally, 0.0001 to 0.001 (ad 0.001 pro dosi! ad 0.003 pro die!) by drops; in mixtures; externally double as much in salves or liniments. 2. *Herba conii*; dose 0.05 to 0.3 (ad 0.3 pro dosi! ad 2.0 pro die!) in powders or pills. Externally for poultices or fomentations; injections or infusion (5.0 to 10.0 : 120.0 to 200.0). 3. *Extractum conii*, soluble in water; in pills, solutions, ad 0.03 to 0.15. (ad 0.15 pro dosi! ad 0.5 pro die!). 4. *Emplastrum conii*, externally as an anodyne. 5. *Emplastrum conii ammoniatum*, made of 2 parts ammon. pulv., 2 parts acet-scillæ, 9 parts emplastrum conii. 6. *Unguentum conii* 1 part extr. conii, and 9 parts ung. cereum.

Sparteine, $C_{15}H_{26}N_2$, the volatile alkaloid of the spartium scoparium, *physiologically* resembles coniine (J. Fick). It is not used medically.

THE TETANIC ALKALOIDS OF THE SEEDS AND BARKS OF DIVERSE CLASSES OF STRYCHNOS, IGNATIUS-BEANS, AND OF OPIUM.

The alkaloids of the seed of the strychnos nux vomica, the barks of lignum colubrinum and the seeds of the Ignatia amara (fabæ St. Ignatii) are, strychnine, $C_{21}H_{22}N_2O_2$, and *brucine*, $C_{23}H_{26}N_2O_4+4H_2O$; the tetanic alkaloid of opium is thebaïne.

Their effect is the same qualitatively; they cause tetanus without paralyzing consciousness, at least directly. They have, therefore, always been called *tetanic poisons.* The other convulsive alkaloids of opium, codeine, laudanine, hydrocotarnin, do not belong in this class, because they narcotize the brain at the same time.

The intensity of the effect of these tetanic poisons differs widely. According to the experiments of Falk junior, the poisonous character of strychnine exceeds all others; its effect is 24 times stronger than that of thebaine, 38 times stronger than brucine, 49 than laudanine, 85 than codeine, and 340 than hydocotarnine. The smallest fatal dose of strychn. nitr. is 0.0006 for a rabbit weighing one kilogramme; of brucine 0.023 grm. In the same way the time of action differs; the smallest fatal dose of strychnine kills three times more rapidly than the smallest dose of brucine; which difference is not produced by strychnine being absorbed more quickly, but because of the milder effect of brucine. As the quantity of the effect of all these alkaloids is absolutely the same, we need only study strychnine, especially as it alone among the others is used medicinally.

The application of the original drugs is not advisable, because the contents of strychnine differs in different samples of the same nut.

STRYCHNINE AND NUX VOMICA.

Strychnine, $C_{21}H_{22}N_2O_2$, forms colorless prisms of a very bitter taste, dissolves in 6500 parts of cold, 2500 parts of hot water, is of alkaline reaction in these solutions, and is absorbed easily by hot diluted aqueous alcohol, benzol and chloroform. The crystallizable salts, as for example strychninum nitricum, $C_{21}H_{22}N_2O_2$, HNO_3, dissolve easily in hot water.

Strychnine *varies between* 0.2 to 0.5 per cent in nux vomica.

PHYSIOLOGICAL EFFECT.

Strychnia is a violent poison which always produces the same symptoms in all animals.

The following table shows the lowest fatal doses for animals, in subcutaneous applications:

	Weight of Animals in Grammes.	Lowest Fatal Dose in Milligr.	According to
Frog	25	0.05	F. A. Falk.
Mouse	25	0.05	"
Rabbit	1000	0.6	"
Cock	380	0.76	"
Whitefish	80	1.0	"
Cat	2080	1.6	"
Dog	3000	2.5	"
Pigeon	270	4.0	"
Man	70000	30.0	Husemann.

The frog and mouse are killed by the smallest, almost infinitesimal doses, and the frog is, therefore, considered as a physiological reagent for the presence of strychnine, doubly so on account of the long duration of the tetanic spasm. The gallinaceæ often withstand extraordinary quantities of the poison, while it is in their crops, probably on account of its slow absorption, and thence were erroneously judged to enjoy immunity from its action (Leube); but very small subcutaneous injections kill them. Rabbits, on the contrary, die more quickly if the poison is taken internally.

Frogs and mice are killed by such very small doses of strychnine, because they are so much smaller and lighter than the other animals. If the dose bore direct relation to the weight, man would be the most susceptible, and the cock and frog the least susceptible to strychnine, according to the following table:

Smallest Fatal Dose, in Milligrammes.	Dose for one Kilogramme.
0.40	Man.
0.60	Rabbit.
0.75	Cat.
0.75	Dog.
2.00	Cock.
2.10	Frog.

But while 1 kilogramme cock is killed by subcutaneous injection of 2 kilogrammes, it requires 50 milligrammes to attain this result through the crop.

Absorption and Secretion.—Strychnine is absorbed by all the mucous membranes, also by the subcutaneous cellular tissue, and can be traced in small quantities in the blood, the medulla spinalis and oblongata, in the pons varolii in

the gray substance of these parts only, the most in the medulla oblongata (Gay), as also a great deal of it in the liver and spleen. The excretion of unchanged strychnine by the urine and saliva (in dogs) begins several days after poisoning, and it requires two to three days until all of the poison is eliminated from the body (*Dragendorff* and *Masing*, *Gay*). Thus it is that if small innocuous doses are given to animals and man continuously, they accumulate in the body until a point is reached where a new, even small dose, causes tetanus. This remarkable cumulative quality demands great caution and forbids continuance of the treatment with strychnine for any length of time. *Leube* and *Rosenthal* assert, however, that, on the contrary, strychnine after being given for a time, establishes habituation, and can be taken in increasing doses indefinitely. Experiments have been made to elicit how long the presence of strychnine could be proven in the corpses of dogs that were poisoned with 0.1 grm., and they showed that chemically it could not be proven any more, but physiologically the bitter taste of strychnine was found 330 days after they were buried and decomposed, and when the tested matter was injected into frogs it produced tetanus. The physiological effect of strychnine was most pure when extracts used were made from the liver and spleen. (Ranke).

As the symptoms of poisoning by strychnine are essentially the same in all animals, we will describe only those in human beings, and will give special attention to the conduct of small doses; and will complete the observations by stating some of its effects on animals.

Strychnine has a very bitter taste which is noted even in 50,000 fold dilution.

An improvement of appetite and digestion has been observed after very small doses of 0.001 to 0.003 grm. repeated daily, the same as in quinine; but we do not credit these assertions for the same reasons that we stated under quinine. So much is sure, that the secretion of saliva is increased, and that long-continued use disturbs the appetite. It is also asserted that after continued use of strychnine the secretion of urine increased, and there is also increased sensibility to impressions on the special senses, especially of the eye and ear, producing thereby a species of discomfort. *Meschede* observed a narcotic effect in man after an injection of 0.001 to 0.008 grm., and also improved disposition and subjective euphoria.

Medium doses (0.005 to 0.01 grm.) produce the following

appearances, either gradually or suddenly (the result of cumulative action): Increased sensibility of touch, so that every feeble touch is felt stronger and longer; formication (Lichtenfels); hyperæsthesia of the retina; dogs shun light and seek shady spots (Falck); "green vision" was observed once (Hemenway); also perversions of the sense of smell. Odors which are usually considered disgusting, as assafœtida and garlic, suddenly appeared agreeable. Then a general indisposition arises; restlessness and fear supervene; finally a feeling of tension and heaviness in the muscles, especially those of the thorax; difficult deglutition. Some muscles, especially the extensors, begin to tremble, principally those of the affected parts in paralyzed people, sometimes without cause, often on very slight irritations. These convulsions last longer and longer, and finally grow tetanic, so that trismus, opisthotomis and stiffening of the extremities arise; respiration is rendered very much labored by spasm of the respiratory muscles, and even is arrested when actual convulsions set in. The face acquires a peculiar, terrified, drawn expression by the contraction of its muscles. Some have observed erection of the penis and even increased sexual desire. Consciousness always remains. Absolute recovery almost always results from these doses in adults after some hours or a few days.

Great fatal doses (0.03 and more) immediately produce symptoms of poisoning, and death ensues in from five minutes to five hours afterwards. The disturbances of the different functions are the same as in the medium doses, only they are more intense. They are: Great anxiety and restlessness, salivation, occasionally vomiting. Suddenly, as if by an electric shock, and sometimes with a violent scream, the poisoned person is attacked with fearful painful tetanic convulsions; the mouth and teeth are convulsively compressed, the neck and spinal column are bent backwards; the feet and arms are stretched flat and hard, as are the muscles of the thorax and of the abdomen, so that the whole body presents an arch bent backwards, rendering respiration completely impossible; the face grows dark red, the veins fill to repletion, the eyeballs protrude, and the pupils are dilated for a time.

Such an attack subsides after a period varying between several seconds and two minutes, respiration begins again, but with continued enormous reflex irritability, so that the *slightest incentive*, a noise or a draught even, causes a re-

turn of the tetanic spasm. No human being can survive three or four such attacks; death comes on by suffocation or by general paralysis.

Influence on Individual Organs and Functions—Brain and Spinal Cord.—Consciousness remains perfect almost until death; but when much carbonic acid accumulates in the blood, this new poison, as in any other suffocation, creates unconsciousness as is usual. Rabbits with artificial respiration gnaw and bite their food quite contentedly if their spinal cord is severed from the head, whilst their body is shaken violently to and fro by tetanic convulsions (Rossbach). The gangliæ of the gray matter in the medulla oblongata and in the spinal cord are placed in a condition of increased excitability, equally affecting the vaso-motor as well as the respiratory and the reflex centres; we will discuss only the latter here. The fact that animals after being beheaded have the characteristic convulsions, proves that these are not caused by a paralysis of nerve-centres in the brain. Another proof is the fact that strychnine convulsions can be somewhat modified by the human will, and by the further fact that the convulsions become more intense with warm-blooded animals after the spinal marrow is separated from the brain (Rossbach). It is not yet decided whether the symptoms are due to a paralysis of the nerve-centres in the spinal cord, or to a diminution of normal resistance of the induction of commotion by one group of nerve-centres on the other group. We therefore consider the most simple explanation of these symptoms as the best, *i. e.*, increased excitability of certain nerve-centres. Very weak peripheral sensory stimulants are sufficient to induce tetanus of a high degree, whilst without strychnine they would not have produced more than a simple convulsive motion. Tetanus is not caused by a different, but by a stronger irritation of the central organ (Freusberg). The frog is thrown into clonic convulsions by an irritation of the ischiadicus, but he becomes tetanic by an electric shock. Normally, the frog reacts on every sensory irritation of the hind legs by flexion; but after strychnine extension only observed. This difference is explained by the fact that strychnine facilitates the extension of reflex action to coinductive passages which otherwise show greater resistance (T. Rosenthal). It is improbable that strychnine-tetanus is caused by a central irritation; probably it is always a reflex. Tetanus never develops if the sensory

posterior roots of the spinal cord of a frog are cut (H. Mayer), or if all external irritation is avoided by careful isolation; on the other hand we can cause tetanus in strychnine poisoning at any time by any irritation. With human beings identical conditions would probably prevail. Strychnine does not act, as S. Mayer thinks, specifically upon the medulla oblongata primarily, but on the whole spinal cord. He was deceived by operating with strychnine immediately after separating the spinal cord. A fresh cut in this cord changes the action of the posterior part so much that such experiments do not prove anything. Whenever Freusberg experimented on animals in which he had cut the spinal cord long before, he could cause tetanus at the same time in the anterior and posterior part of the animal.

If the animals do not die during the tetanus, as, for example, frogs, because they cannot suffocate; then they finally perish from paralysis of the same central parts which were most irritated in the beginning.

Peripheric Nerves.—It appears probable that the terminals of the sensory nerves are put in a condition of increased excitation, judging from experiments which men made on themselves.

The sense of vision is especially changed (v. Hippel) as follows: The field of colors for blue (not for white, Cohn) is enlarged in the eye corresponding to the side on which the injection of strychnine was made; vision is temporarily enhanced; the border for the recognition of certain distinct points is moved more towards the periphery; the field of vision is increased.

The favorable results that strychnine obtained in amaurosis (Nagel) are another proof for a direct influence on the optic nerve; as also, if Nagel's observations of partial cure of "nervous" deafness be confirmed, it would be because of its influence on the auditory nerve.

The *motor nerves* and nerve-terminals are as little influenced as the muscles; where the nerves are cut, the extremity concerned remains free from convulsions, and paralysis steps in by over-excitement after long convulsions, the same as after any other great excitement or exertion; the muscles have an acid reaction immediately after death; this is found even when the heart is still beating. Therefore, rigor mortis is quickly established.

The *nerve-centre* which *controls respiration* is primarily agi*tated* violently, so that even small doses cause difficulty of

breathing, whilst large doses cause tetanic convulsions of the respiratory muscles, suspension of respiration in the act of inspiration, spasmus glottidis and even death by suffocation.

The *circulation* shows the following changes: First, change of all peripheral vessels (real tonic convulsion of arteries in cold and warm blooded animals) and great increase of the blood-pressure. The last is the result of various causes; partially the purely mechanical, strong and long-continued convulsions of the whole system of transverse muscles, whereby great trunks of arteries may be compressed, and the resistance to the blood by the convulsed muscles (Sadler); then we observe, in cases of cessation of respiration, a paucity of oxygen and an abundance of carbonic acid gas in the blood, which conditions increase the blood-pressure; finally, in consequence of a direct violent irritation of the vaso-motor centre, as is shown by the experiments of S. Meyer on animals under the influence of curare and artificially respirated, where (without convulsions and dyspnœa) enormous blood-pressure ensues; after the spinal cord is cut below the vaso-motor centre, the increase of blood-pressure in such animals is hardly observable. The action of the heart in frogs is considerably slower during convulsions until it actually is arrested; in warm-blooded animals it is accelerated, probably in consequence of the enormous efforts of the muscles, in the same way as in other rapid motions, as in running, gymnastic exercises, etc.

In animals under the influence of curare, we see slower pulse however, as S. Mayer showed, caused by primary irritation of checking apparatus of the heart.

The *temperature* rises during the convulsions, sometimes as much as 2° C. (Falk).

Digestive Organs.—The effect which small doses are said to produce on the appetite is very doubtful. Thus far, we record: Salivation, pale color of the stomach and intestines by contraction of the arteries; contraction of the spleen; but no increase of the peristaltic motions.

The *secretions of the kidneys*, of the sudoriparous and of the salivary glands are said to be increased.

The *cause of death* may be twofold; either by suffocation in an attack of tetanus or by general paralysis. The heart survives the other organs.

Manner of Action of Strychnine.—It retards decomposition and fermentation like quinine; it also acts more perniciously on the lowest organism, like quinine; it also acts

on the albuminates, like the alkaloids. There is therefore no reason to look for its influence on the cells of the higher animals, for it affects these just like the other alkaloids do. But we can use these qualities less, because it affects the general organism of the higher animals so perniciously.

Harley has proven that, by mixing blood with strychnine, the blood elements are prevented from absorbing oxygen and secrete carbonic acid, and that this also occurs in the living body. But we must not deduce its tetanic effect from this change of the quality of the blood, because salted frogs without heart and blood, (Bernstein-Lewison) are attacked by the same tetanus. Neither can we ascribe the convulsions to hyperæmia of the spinal cord, which has so often been observed.

The only reason for the convulsions of strychnine is therefore a direct influence of the nerve-centres. This effect is supported and increased by the other effects and the indirect consequences; as, for example, the increase of carbonic acid, alone, causes increase of blood-pressure and general convulsions; thus the effect of the carbonic acid, the contracted muscles, etc., must be added to those of strychnine. We have also observed, as Falk states, firstly, that clonic convulsions may follow tetanic convulsions, and for a long time we considered the latter solely as a result of the action of the carbonic acid—*i. e.*, as convulsions from suffocation. But the fact which we found later, that such clonic convulsions happen also in rabbits under artificial respiration, has shaken this opinion; they are therefore, perhaps, solely the result of the gradual relapse from the abnormally increased irritability.

THERAPEUTIC USE.

Strychnine was formerly used a great deal in paralysis, because of its physiological effects; but it is less used now, as is quite proper; because, first, its effect on paralysis is very slight; then its use is not unaccompanied by dangers, especially on account of its cumulative action, and lastly we possess to-day a much more effectual and less dangerous remedy in electricity.

Cases are constantly reported, by good observers, in which injections of strychnine effected cures in spinal and *peripheral paralysis*. But these cases are so few in proportion to the great mass of failures, that they cannot alter our

opinion, but they should encourage new experiments with the assistance of the present facilities for diagnosis, to elicit an exact knowledge of the conditions which demand and respond to strychnine.

In cerebral paralysis strychnine has proven useless. It often proved injurious when given too early in anatomical lesions (especially hemorrhages).

The majority of observers agree to-day that strychnine should be avoided in all spinal processes and paralysis of an irritative and progressive character, as in the various forms of myelitis, tabes dorsalis, spinal irritation, etc. It may be tried in completed cases, and then perhaps with some chance of success. No sure opinion can be formed as yet of its efficacy in so called "reflex paralysis," notwithstanding Brown-Séquard's warm indorsements. The first signs of effect that appear in the paralytic parts are sensations of tension and slight twitchings. Strychnine proved useful in lead palsy and some few isolated cases of peripheral paralysis. (Andral, Tanquerel.) It may, therefore, be used for such cases, when other remedies, especially electricity, have failed. It is also claimed that it acted favorably in some cases of rheumatic paralysis. Some successful cases reported by Barwell do not present a sufficiently clear ætiology. He lays great stress on injections in local attacks and on a small single injection (to have a small surface of absorption) of a strong, concentrated solution.

Some observers have used it with good effect in prolapsus recti of adults and children, and in incontinentia urinæ, caused by atony of the muscles of the bladder.

It is seldom used in anæsthesiæ, and much effect could hardly be expected from it on account of its physiological effect. We may yet mention chorea for which strychnine was praised by Trousseau. Others (See and Sandras) could not verify his favorable reports.

Another field has recently been opened for the therapeutic use of strychnine. In former years, especially English physicians, tried strychnine in "amauroses." Nagel now reports occasional surprisingly good results with strychnine in that disease. He describes especially the essential amauroses as a good field for its application in subcutaneous injections in the temporal region, when the optic nerve is not materially changed, and also in toxic and traumatic amblyopias and amauroses (anæsthesia retinæ). Even after

atrophic degenerations of the papilla optica had set in, decided improvements of vision were observed, and also a partial restoration of the anomalous ophthalmoscopical appearances. This will happen especially, as Leber says, if the pathological process has run its course, whilst in its progressive stages, nothing can be expected. In spite of several reports to the contrary, there are enough positive assertions to admit of no doubt that many cases of cure of amblyopia are due to the effect of strychnia, judging from its physiological effects. We must ascribe this result to its peripheral effect on the optic nerve. The best way to apply it is in the form of subcutaneous injections into the vicinity of the diseased eye, once daily, in increasing doses of 0.001 to 0.005 grms.; if there is no improvement after several injections, then it will be useless to continue.

Preparations of nux vomica are often used in dyspeptic complaints, in the same conditions as quinine and the aromatic bitters. We again refer to our remarks on quinine, and state only that strychnine is even more useless as a "stomachicum," because it may become very dangerous.

Strychnine preparations are also given after diarrhœa, especially in chronic intestinal catarrh with many thin discharges. Good results are mentioned, but it seems difficult to reach a conclusion, for it was usually administered in combination with opium.

It has nevertheless been prescribed in the opposite state of the bowels—in chronic constipation. Here also there is the same uncertainty on account of its customary combination with aloes, rhubarb, and similar drugs. It is well to give strychnine as little as possible for these purposes, in view of the uncertainty of its effect and the ever-present danger of strychnine poisoning.

Dosage and Preparations.—1. *Strychninum*, properties given above (ad 0.01 pro dosi! ad 0.03 pro die!).

2. *Strychninum nitricum.*—Delicate, flexible, silky, white, brilliant crystals, very bitter; soluble in three parts of boiling, sixty parts of cold water, difficultly soluble in absolute, more readily in dilute alcohol. The aqueous solution has a neutral reaction. Used in powders, pills, alcoholic or aqueous solution. It is given in increasing doses beginning with 0.001 to 0.005 per dose, twice daily (ad 0.01 pro dosi! ad 0.03 pro die!). The dose for children is 0.00025 to 0.0005. The effect of strychnine varies greatly in different individuals, and careful attention is necessary in using it, especially as cumulative action may easily take place.

In hypodermic injections the doses are the same, Str. sulphuricum, str. hydrochloratum, str. aceticum, are not officinal. Their doses are the *same as those of str. nitricum.*

3. *Semen strychni* (nux vomica) is best entirely avoided because of its varying percentage of strychnine (ad 0.1 pro dosi! ad 0.3 pro die!).

4. *Extractum strychni aquosum.*—A yellowish-brown powder, difficultly soluble in water, which it discolors to a turbid greenish white. 0.03 to 0.1 in powders, pills, solution, several times a day (ad 0.2 pro dosi! ad 0.5 pro die!). The dose for children is 0.003 to 0.01.

5. *Extractum strychni spirituosum.*—Brown, soluble in water, which it renders turbid, very bitter. Given internally in powders, pills, solution, from 0.01 to 0.05 (ad 0.05 pro dosi! ad 0.15 pro die!). Dose for children, 0.0005 to 0.005.

6. *Tinctura strychni.*—1 part str. to 10 parts spiritus vini rectific. 5 to 10 drops several times a day (ad 0.5 pro dosi! ad 1.5 pro die!).

7. *Tinctura strychni ætherea.*—1 part str. to 10 parts spiritus æthereus. Given like the preceding.

Treatment of Strychnine Poisoning.—Two objects must be accomplished. The poison which may still remain in the stomach must be removed or rendered harmless, and the symptoms which arise from absorption and from the action upon the central nervous system must be combated.

The most ready means of attaining the first object is the application of emetics. The stomach-pump may also be employed shortly after the poison has been taken, but this, like any other mechanical irritant, is apt to increase the tetanus if the convulsions have commenced.

Tannic acid and substances containing it are useful as direct antidotes to as much of the poison as remains in the stomach. Tannic acid forms a compound with strychnine which, though difficultly soluble in water, is easily dissolved by alcohol and acid liquids, such as the gastric juice. Emetics are therefore still indicated after the antidote has been given. Tincture of iodine (beginning with 10 to 20 drops given in water every ten minutes) is also recommended as a direct antidote. Cathartics should be employed in addition to the emetics. The fatty cathartics are most beneficial, especially castor or croton oil. The remedies and rules which have been recommended for the treatment of strychnine convulsions are exceedingly numerous. Venesection, though it delays the tetanic convulsions in rabbits (Vierordt, Kaupp), does not prevent them and is therefore useless. The observation of Kunde that tetanus is promoted by refrigeration if small quantities of strychnine have been taken, and by heating if the quantity of poison is large, is of no special practical value.

The employment of artificial respiration appears of greater importance, as was first suggested by Richter and since studied by Rosenthal, Leube, Uspensky, and Ebner. But the investigations of Rossbach and Jochelsohn have shown that though artificial respiration and a condition of apnœa may diminish the violence of the convulsions and prolong life, they are powerless to save the latter when the dose of strychnine is in itself sufficient to cause death. No determination of this question has been given in practice. Whether the observation made by J. Ranke that the convulsions are suppressed by the application of a constant galvanic current to the spinal cord (the direction of the current is immaterial) has any practical value, is undecided.

Far better results are obtained from the use of certain drugs. Most of the so-called narcotic poisons, atropine, hyoscyamin, aconitin, physostigmin, nicotine, morphine, cannabis indica, bromide of potassium, and curare have been tried in strychnine. We refrain from a minute description, as no certain result has been shown to follow their use. They are

now almost abandoned. According to the foregoing experiments they are all rendered superfluous by the inhalation of chloroform and by the use of chloral hydrate. It has been pointed out by Liebreich and confirmed by Rajewsky, Schroff, and Hausemann that chloral hydrate can save animals which have taken quantities of strychnine that would otherwise have been fatal.

The Alkaloids of Some Classes of Veratrum.

The alkaloid veratrine is the active principle of the white hellebore (rhizoma and root of veratrum album or helleborum album, colchicaceæ), of sabadilla or Mexican lousewort (semina sabadillæ, from veratrum officinale, Schlecht, or sabadilla officinarum, Brandt), and of veratrum viride, especially of the rhizoma. Veratrine is distinguished from all other poisons by a very noteworthy action upon the substance of the striped muscles of the heart and frame, and especially by an enormous prolongation of the curve of contraction. Buchheim and Weyland, indeed, thought they had proved that sabadillin, delphinin, emetin, aconitin, and sanguinarin have a similar effect, but the statement is erroneous according to Boehm and Ewers. The statements made concerning the alkaloids of veratrum sabadilla are widely at variance, probably because decomposition and changes occur during the process of extraction and purification. Wright and Luff obtained the alkaloids by percolating the bruised seeds with alcohol containing acetic acid, evaporating, separating from the resinous portion, and repeatedly shaking the solution with ether. In this way they obtained three alkaloids: (1) veratrine $C_{32}H_{52}NO_{11}$, identical with that described by Conerbe. This on saponification yields acid dimethylprotocatechu (identical with Merk's veratric acid), and a new base, veratrin $C_9H_{15}NO_3$. (2) *Cevadin* (Merk's veratrin) $C_{32}H_{49}NO_9$. This on saponification yields methyl-crotonic acid and cevin $C_{27}H_{43}NO_8$. (3) *Cevadillin* $C_{24}H_{33}NO_6$. O. Hesse gives the following formulæ for the alkaloids of sabadilla seed: sabadillin $C_{21}H_{35}NO_7$, sabatrin $C_{26}H_{43}NO_9$, and veratrin $C_{32}H_{51}NO_9$.

The plant is no longer used directly, on account of its varying proportion of active substance and the facility with which veratrine is obtained.

Veratrine.

The alkaloid veratrine prepared from the white hellebore and seeds of *sabadilla*, occurs either as a fine white crystalline powder or in long, colorless prisms.

It is insoluble in cold, slightly soluble in hot water (1 part in 1000), readily soluble in alcohol and ether. It unites with one equivalent of acid to form partly crystalline, partly gum-like salts, which are easily soluble in water.

PHYSIOLOGICAL ACTION.

Veratrine is one of the few alkaloids which not only act upon the nervous system and the muscles but also produce inflammation of the skin and mucous membranes. It has a very poisonous effect upon men and all classes of animals, both warm- and cold-blooded, even in doses of from 0.005 to 0.01 grm.

0.03 grm. cause death in rabbits in a few minutes; in cats 0.005 grm. are fatal in two hours. The fatal dose for men is not determined, but from 0.005 to 0.01 grm. act with great violence in all cases.

Absorption and Excretion.—It is not certain that veratrine is taken up by the uninjured skin. This is probable, however, since the sensory nerves of the skin are violently stimulated when veratrine is rubbed upon it. It is also stated that general symptoms appear after this treatment. When applied to the mucous membranes it always passes into the blood, though not very rapidly. It has afterwards been found in many internal organs, and very soon reaches the heart.

Symptoms in Men.—Veratrine rubbed upon the skin in the form of ointment creates a feeling of heat, pricking, burning, increased sensibility followed by a decrease thereof, red spots on the skin, and blisters. Taken into the nose it produces violent and long-continued sneezing, bleeding, and catarrh. When inhaled it causes a protracted and spasmodic dry cough. In the mouth and throat it produces a sharp, biting sensation and reflex increase of salivary secretion. The pain in the throat is often so great that swallowing is difficult or impossible.

In the stomach small doses (0.003 grm.), and still larger ones (0.005 to 0.03 grm.), produce a feeling of warmth which soon becomes one of burning, also nausea and violent vomiting. The latter removes most of the drug which is not absorbed rapidly. Afterwards violent pains in the intestines and evacuations take place, the fæces, as well as the discharge from the stomach, being often mixed with blood.

The pricking, burning sensation in the stomach soon

extends over the entire body and there is a "creeping" feeling in the extremities. Respiration becomes slow and difficult, the pulse infrequent and irregular, and the temperature falls. Severe headache without loss of consciousness, dilatation of the pupils, involuntary muscular contraction in various parts of the body, and a swoon-like collapse follow. A fatal termination has been observed only twice in the human species (Nivet and Girand, in the case of two young men poisoned by their sisters). Death was preceded by marked symptoms of weakness, almost imperceptible pulse, and loss of consciousness.

Effects upon Individual Organs and Functions of Men and Animals.—We consider first, as specially characteristic of veratrine, the effects upon the peripheral nerves, the striped muscles, and the heart.

The first effect of most other alkaloids is upon the central nervous system and the seat of sensation. This effect is generally so intense that the irritability of the peripheral sensory nerves can no longer be investigated, because even long-continued sensory impulses have no action on the centre. The first effect of veratrine, on the contrary, is violent stimulation of the sensory-nerve terminations in the skin and mucous membrane, producing, by reflex action, sneezing, coughing, or the feeling of pricking, burning, and itching of the entire skin and all mucous membranes, whether the application be local or general through the circulation.

Of the greatest interest is the action of veratrine on the striped muscles and motor nerves in both cold- and warm-blooded animals. This was first observed by Kölliker. For example, if a trace of veratrine (0.00005 grm.) is introduced beneath a frog's skin, all his actions are greatly changed. His usual progression by long leaps becomes a slow and difficult creeping, as though he had become a different creature. Several seconds elapse before the animal is able to extend his hind legs. His motions are powerful and elastic, but he is unable to leave the spot. Still it is evident that the motor impulses are not retarded, for if the hind leg is held close to the body, the extensor muscle may be clearly seen under the skin in the act of commencing the extension. As during this time the contractor muscles also act violently, the leg assumes a median position, and then very gradually becomes fully extended. This slow motion gives the frog a

strange, almost weird appearance, since the sudden transformation of the entire mass of striped muscles into smooth bundles of fibres renders the motions of the limbs the slowest possible to imagine. The beginning of contraction is not delayed, but the transition from contraction to repose is retarded and rendered more difficult (von Bezold). These changes are not so evident with larger doses, because the heart is soon paralyzed, and hence less poison is conveyed to the muscles. Death, moreover, soon ensues. In warm-blooded animals, likewise, the muscles are seen to stiffen and a protracted condition resembling a convulsion occurs, followed by great motor weakness.

Experiments made on frog's muscle in this condition show the following changes in the curves drawn:

The duration of latent stimulation is normal; the muscle contracts rapidly to the maximum. Sometimes the motion is less rapid as the maximum is approached. The time occupied in attaining the maximum is never much longer than with a normal muscle. The period of extension, however, and hence the falling curve, is from 40 to 60 times as long as with the normal muscle. The curve approaches the line of abscision very slowly (Kölliker, von Bezold, Fick, and Boehm). The same form is obtained whether stimulation is direct or through the nerves. If the impulses, however, whether communicated by the nerves or caused by direct application of the electrodes to the muscle, are too numerous and in too quick succession, the muscle assumes the normal condition for a time, so that subsequent momentary stimulation produces only brief contraction. If the muscle is then allowed to rest, the veratrine condition reappears (von Bezold, Fick, and Böhm). The contraction of muscle under the influence of veratrine is not only of longer duration than the normal but two or three times as great, both in cold- and warm-blooded animals.

The curve, therefore, especially with living warm-blooded animals (rabbits, cats, and dogs), attains twice or thrice the normal height for the same intensity of stimulation. In like manner a muscle of a warm-blooded animal which has been greatly fatigued by many thousand maximal contractions can be restored by a small quantity of veratrine, so that it will undergo a four-fold greater contraction than immediately before.

This restoration, due to veratrine, frequently lasts very

long, and the curve of fatigue returns very gradually to its height before the restoration (Rossbach and Harteneck). The contraction of frog's muscle under the influence of veratrine also generates much more heat than a normal contraction (Fick and Böhm).

The passive, blood-traversed, living frog's muscle is first lengthened, then shortened, after poisoning with veratrine. In both conditions the extent and completeness of elasticity are diminished, but this is merely a result of changes in the contractile cells (Rossbach and Anrep).

Formerly, veratrine contraction was described as a simple tetanus; that is, an oscillatory condition of the muscle in which stimulation takes place in separate and periodically recurring spasms, the intervening pauses being so short that the muscle has not time to recover its natural length. This, however, is incorrect, since, if veratrine contraction were tetanic, the galvanoscopic frog's leg would immediately fall into a condition of secondary tetanus upon placing its nerves in contact with the active muscle. Fick and Böhm repeatedly placed nerves of the highest sensitiveness in contact with muscle under the influence of veratrine, but they never found a trace of secondary tetanus. The veratrine-contraction is therefore only a simple, greatly prolonged contraction. It is easily shown that the altered action of muscle treated with veratrine, depends merely upon a change of properties of the muscular substance and not upon any alteration of the nervous current, since curarized muscle in which the motor-nerve terminations are paralyzed upon treatment with veratrine falls into the same condition and exhibits the same changes in magnitude and duration of contraction that are shown by normal muscle so treated (Kölliker). The nerve-current, besides, is entirely normal in veratrine poisoning (Fick and Böhm). And that the change in muscular activity in living animals is not due to altered innervation from the spinal cord is evident from the circumstance that all the characteristic effects of veratrine upon muscle may be produced after injury to the spinal cord. They may even take place on the same side on which the motor nerve has been cut.

Two quite different views may be taken of the nature of the muscular condition produced by veratrine.

The first is that the presence of veratrine in the muscle favors the initial chemical action which is the cause of con-

traction, so that the contracting substance is formed in greater quantity upon momentary stimulation. According to the other view, the process of restitution, which is the basis of muscular relaxation, is delayed and made more difficult by the presence of veratrine. Fick inclines to the former view, in consideration of the increased generation of heat that he observed in muscle affected by veratrine. The very great increase of muscular contraction observed by us points to the same view. We cannot, however, absolutely exclude the other theory, and there is no apparent reason why both processes may not take place simultaneously in the muscular fibres. If the dose is relatively very large (0.003 to 0.005 grm.), the muscle finally becomes deprived of direct irritability and is paralyzed. After small doses the motor-nerves retain their irritability well for a long time.

We [Rossbach and Clostermeyer] think that we have disproved, by the following experiments, the existence of the initial increase of irritability as stated by Von Bezold. If rabbits are so slightly curarized that weak muscular contractions can still be produced when the induction-current on opening circuit is transmitted to the muscle from the nerve-trunk, subsequent injection of small quantities of veratrine makes the maximal contraction on indirect stimulation rather smaller than before, while with the smallest direct stimulation the contractions are exceedingly high and show all the veratrine characteristics. Only after the use of very large quantities of veratrine do the terminations of the motor nerves become paralyzed, as if poisoned by curare, while the muscle itself can still be thrown into slight contractions and the nerve trunk still shows an entirely normal variable negative current.

Muscle of the Heart, and Circulation.—The muscle of the heart in cold-blooded animals is affected by veratrine in exactly the same way as are the other muscles. If the heart is removed from the body and made to register its contractions by Coats's method, the curves might be mistaken for those of the striped muscles, having no more of tetanic character than the latter (Böhm).

If a frog is poisoned with doses of from 0.0005 to 0.05 grm., the first effect is a very gradual diminution of the number of beats, commencing 20 or 30 seconds after the injection. The duration of the systolic contraction becomes longer and longer, and at last complete systolic pauses, lasting

20 or 30 seconds, occur, so that the frequency of the pulse falls to half the normal. The death of the heart does not occur until two or three hours later, long after life has ceased in the rest of the body. It is remarkable that towards the end, while the heart still contracts spontaneously, there is a period in which the most powerful external stimuli are unable to cause contraction. Stimulation of the exposed vagi, stimulation of the venous sinus, and, finally, poisoning with muscarine, have not the smallest effect on the activity of the heart poisoned by veratrine. Stoppage of the heart caused by muscarine is immediately removed by veratrine. But the characteristics of veratrine poisoning in the heart cannot be removed or mdoified in any way by physostigmine, atropine, or curare (Böhm).

It is said that much greater resistance to the action of veratrine is offered by the heart of the rana esculenta than by that of rana temporaria (Prevost).

In warm-blooded animals (rabbits and dogs) the smallest doses of veratrine (0.0001 grm. injected into a vein or 0.001 under the skin) cause an immediate acceleration of the heart's beat and increase of blood-pressure. Moderate and large doses (0.001 to 0.01 grm. injected into a vein or 0.005 to 0.04 under the skin) immediately slow the pulse, lower the blood-pressure, and finally produce irregular action and paralysis of the heart. Bezold and Hirt derive all these changes from an initial stimulation and subsequent paralysis of the vaso-motor centre and of the regulating motor nervous apparatus of the heart; but this view involves many contradictions. Braun, from exact experiments, is led to deny the existence of paralysis of the vaso-motor centre. It is probable, also, that the chief action of veratrine in warm-blooded animals is directed towards the muscle of the heart rather than the nerves. In febrile human patients veratrine is followed by a diminution of from 20 to 60 beats in the frequency of the pulse.

Central Nervous System.—The action in this is as good as unknown, as the independent peripheral muscular changes prevent the occurrence of a well-defined reaction of the centre. Formerly, indeed, the remarkable changes in the motions of the animals and the muscular contractions were considered as proceeding from the centre, which was certainly an erroneous opinion. On the other hand, we cannot avoid considering the brain and spinal cord as influenced also, seeing that they are always finally paralyzed, and that cer-

tain parts at least, such as the vagus centre in the brain and, to some degree, the vaso-motor and respiratory centre, exhibit initial stimulation. Further experiments are required to show how much of this effect must be ascribed to veratrine and how much to weakness of the circulation (in warm-blooded animals). Consciousness is always preserved for a long time, even until near death.

The respiration of the animal is at first accelerated by very small doses of veratrine, this effect gradually disappearing.

Bezold deduces this from stimulation of the sensory-nerve terminations in the lungs, as the effect is not destroyed when the cervical vagus is severed.

Larger doses, under all circumstances, produce diminution of frequency and finally complete stoppage of respiration, in consequence of paralysis of the pulmonary branch of the vagus and of the respiratory centre situated in the prolongation of the cord. Respiration after veratrine posioning, according to Bezold, is very convulsive, with very long expiratory pauses. It greatly resembles respiration after severance of the vagus.

The blood, however, despite the gradually increasing incompleteness of aeration, appears not to darken so rapidly as in normal animals with incomplete respiration.

The temperature falls both in healthy (Braun) and in feverish animals and men (Drasche, Kocher); in the latter from 1° to 3° C., probably on account of decrease of circulation.

Digestive Organs.—The increase of salivary secretion is always reflex. The vomiting and diarrhœa, as the substances removed are often bloody, must be ascribed in part to a strong stimulation and hyperæmia of the mucous membranes. Vomiting and diarrhœa, however, occur also after hypodermic injection.

THERAPEUTIC APPLICATION.

The white sneezewort, which was much employed even in the time of Hippocrates has recently fallen into disuse. Its place was taken by the alkaloid, which, especially in pneumonia, rapidly came into favor a decade ago, but is now rightly abandoned. At the present day we know of no affection in which this drug is of certain and infallible benefit or enjoys any special advantage over other sub-

stances. The circumstances in which veratrine is still occasionally used are as follows:

In neuralgia it is of no benefit when given internally, but external application may sometimes lessen the severity of the pain. It is especially recommended in neuralgia of the fifth pair. It is not proved that it is of greater benefit in some forms of neuralgia (as was assumed with regard to the so-called rheumatic form, for example) than in others. Experience shows that it does not cure the disease but only diminishes the pain, and not always even this. This result is produced especially when its administration causes a feeling of warmth and pricking in the skin. It is very difficult here, as so often occurs in passing judgment on a drug, to arrive at a correct result, because of a multitude of contradictory statements. While Turnbull, Oppolzer, and many others highly recommended veratrine in neuralgia, Hasse, Romberg, and other observers consider it only as a palliative or as entirely useless. We ourselves have not found it to have any beneficial effect.

From the foregoing we may conclude that if more reliable remedies fail, veratrine may be tried. The use of veratrine as an antifebrile in the most widely varying acute febrile affections, especially pneumonia crouposa, which came into favor some fifteen years ago, is almost entirely abandoned at present. We therefore make only the following brief mention of its effects:

The one certain result of veratrine is rapid and considerable diminution of the frequency of the pulse. The effect on the temperature is variable and uncertain; the extent of infiltration, the total duration of the process, and the mortality are not affected. The vomiting and diarrhœa sometimes produced are unpleasant, and collapse, often occurring without any warning, may be directly dangerous.

It is best not to give veratrine at all in croupous pneumonia. If it is used it should only be in violent fever, especially if this is out of proportion to the local process, not in the course of subacute pneumonia. It is directly contraindicated in low fever, rather pronounced local affection, and great debility. The experiments in the action of veratrine in other acute febrile affections are less extended.

In erysipelas and acute rheumatism, it reduces the pulse and temperature as in pneumonia. In other respects no *positive decision* can be made.

In typhus fever, as Wachsmuth has shown, it is not only useless as a febrifuge, but directly injurious because of production of collapse.

The other effects that have been claimed for veratrine have in part been not confirmed (diuretic), in part can be produced by less dangerous medicines. As has already been mentioned, veratrine is employed *externally* in neuralgia. The rhizoma veratri, on account of its powerful effect in producing sneezing, is a constituent of many sternutatories. It was formerly used in itch, but is now replaced by more reliable and less dangerous remedies.

Dosage and Preparations.—1. *Rhizoma veratri*, given internally, 0.03 to 0.2 pro dosi (ad 0.3 pro dosi! ad 1.0 pro die!), in powders, pills, infusion, and decoction; applied externally as a salve (1 part in 6 or 8); as a sternutatory, 1 part to 15 or 20 parts of some inert powder.

2. *Veratrinum, veratrine*, 0.001 to 0.005 pro dosi (ad 0.005 pro dosi! ad 0.03 pro die!), given in pills or troches. It is not given in powder or solution on account of excessively severe local action on the mouth and pharynx. Used extensively in salves (0.2 to 0.3 : 5.0) and alcoholic solution (1.0 : 15.0).

3. *Fructus seu semina sabadillæ* (Mexican lousewort), which contain *veratine*, are used only externally, in decoction (5.0 : 200.0 of water or vinegar), as a wash for pediculus capitis. As in the use of helleborus albus, care must be taken to avoid absorption by injured portions of the skin, as symptoms of general poisoning may be produced (ad 0.25 pro dosi! ad 1.0 pro die!).

Treatment of Veratrine Poisoning.—When taken into the stomach, veratrine itself generally causes violent vomiting which removes a large part of the drug.

Tannin may be given as an antidote.

Opium is indicated in excessive diarrhœa.

In addition to these, the most important task is the treatment of the weakness of the heart, which must be combated by the strongest means of stimulation.

APPENDIX TO THE ALKALOIDS.

In the main part of this section we have discussed those alkaloids that are of physiological interest and greatest therapeutic importance; we shall now consider briefly those of no special physiological or therapeutic value.

In the root of the monkshood (aconitum napellus, ranunculaceæ, and many other species of monkshood) the most effective and best investigated constituent is aconitin, $C_{30}H_{47}NO_7$ (also called *German aconitin*).

In addition to this, several other active but not well-known bodies (aconellin, acolyctin) are found in the same root.

Physiological Action.—Aconitine in a dose of 0.01 grm. is fatal to the frog; 0.05 grm. to the rabbit. It is not, however, among the strongest alkaloids. When taken internally it produces severe burning pain in the

mouth, œsophagus, and stomach; nausea, eructations, rumbling in the bowels, followed by general feeling of heat and redness of the face. An hour after the drug has been taken there is a crawling sensation in the whole body, with other special subjective sensations of various kinds, which give place to general anæsthesia. Thereupon severe pricking pain is felt in the first branch of the trigeminus, together with headache, vertigo, singing in the ears, photophobia, dilatation of the pupils, apathy, and loss of memory. The heart's beat after transient stimulation becomes slower and slower (because of extremely complicated, not yet understood disturbances in the innervation of the heart), and afterwards becomes irregular, intermittent, and completely paralyzed. The blood-pressure continues to fall.

Respiration is retarded from the beginning, and at the same time becomes deeper (convulsive expiration). As death approaches the frequency of respiration continues to diminish and finally ceases. The internal and external temperatures also continually diminish. Great lassitude and muscular weakness and a feeling of muscular rigidity render locomotion and the erect posture impossible, probably on account of paralysis of the motor-nerve terminations.

Böhm's objection to the statements of Achschamurow, who found (in frogs) a complete paralysis of the terminations of the nerves, was subsequently retracted in the case of the rana temporaria at least.

The action on the brain and sensory nerves has not been closely studied. Consciousness is long retained. In frogs the organs of voluntary and reflex motions are soon paralyzed (Fleming, Schneller and Flechner, Schroff, L. von Praag, Achschamurow, Böhm, and Wartmann).

In the *roots of the aconitum ferox* is found *pseudaconitin*, $C_{36}H_{49}NO_{12}$ (formerly also called English aconitine, napaline or napelline). The action of this is qualitatively like that of German aconitine, but about 17 times as intense.

The diminished sensibility to tactile impressions and heat caused by local application of pseudaconitin (Böhm) is also found when German aconitine is employed (Schroff).

The *treatment of aconitine poisoning* is the same as that of poisoning by nicotine, to which we therefore refer.

Therapeutic Application.—Aconitine may be entirely dispensed with. It was warmly recommended by Störk in most diverse circumstances, but its application has suffered continual restrictions, until it is now given in general only in two diseases, and in those with very small benefit.

The first is neuralgia of various nerves, especially neuralgia trigemini. No exact formulation of its ætiology can be drawn from the experiments that have been made. It has been given in neuralgia which was ascribed to a "rheumatic cause," as well as in very old cases whose nature was quite obscure; beneficial results have sometimes followed.

It has been recommended principally by English and American physicians (Brodie, Turnbull, Watson), some of whom found it useful when given internally, others when externally applied (aconite ointment). The older German observers (J. Frank, for example) found it quite useless in neuralgia of the fifth pair and *ischias*.

In recent times it has been seldom used, and with little benefit (Erlenmeyer, Pletzer, and many others).

With reference to external application, it must be observed that *German aconitine is* entirely ineffective when applied to the skin, according

to some observers. In neuralgia, therefore, when other medicines are without effect, aconitine may be employed as an empirical remedy; and indeed it seems to have been of service in some cases. The use of aconitine in *rheumatism* was formerly very extended. It was recommended in acute rheumatism of the articulations and muscles on the one hand, in chronic cases on the other.

It was deemed especially efficacious in reducing pain and fever in acute rheumatism. It is now rendered entirely superfluous by salicylic acid, and its utility in the chronic form of the disease is also more than doubtful. Its value in the treatment of gout is likewise by no means assured, according to Garrod.

Dosage and Preparations.—1. *Tubera aconiti.* 0.03 to 0.1 pro dosi (ad 0.15 pro dosi! ad 0.5 pro die!), given in powders or pills.

2. *Aconitine*, little used internally (ad 0.004 pro dosi! ad 0.03 pro die!).

3. *Extractum aconiti*, given in pills and solution (ad 0.025 pro dosi! ad 0.1 pro die!).

4. *Tinctura aconiti*, 5 to 15 drops (ad 1.0 pro dosi! ad 4.0 pro die!).

STAVESACRE—semina staphisagriæ obtained from delphinium staphisagria, contains, according to Dragendorff, four alkaloids: *delphinine*, *staphisagrine*, *delphinoidine*, *delphisine*.

Delphinine, $C_{23}H_{35}NO_6$, acts principally on the respiration (death from asphyxia), on the circulatory organs (diastolic stoppage of the heart), on the spinal cord (convulsions with rapidly progressive general paralysis and insensibility). The motor nerves long remain unparalyzed. The muscles fall into intense fibrillary contractions (Böhm).

In toxic action it closely resembles the aconite alkaloids, from which it is distinguished only by its energetic action on the vascular nerves, which is but slight produced by aconite.

Staphisagrine, $C_{22}H_{33}NO_4$, has a paralyzing effect upon the frog similar to that of curare and produces no muscular vibration or stoppage of the heart.

In warm-blooded animals it does not produce the violent convulsions that follow delphinine; still death from asphyxia is caused by this alkaloid also (Böhm). No investigations of delphinoidine and delphisine have been made. All the above-mentioned alkaloids and preparations of plants in which they occur find, or at least deserve, no therapeutic application.

GLYCOSIDES WITH STRONG PHYSIOLOGICAL ACTION.

The substances chiefly derived from the vegetable kingdom which are called "glycosides" in chemistry have this in common: that when boiled with weak acids, or when acted on by organic ferments they are separated into sugar and a second substance which may differ materially in the

different glycosides. But, as they are very sharply distinguished from one another in other chemical regards, so also do they differ in physiological effects, some being practically of no strength, or at most very weak, others acting as poisons on the animal organism, like the most powerful alkaloids. Among the weak glycosides are those of the group of the benzol derivatives, for example salicin and tannin; others, as convolvulin and jalapin, belong to the laxative compounds, in so far as their physiological action, etc., is similar to that of these substances.

In this connection we shall consider the powerfully poisonous glycosides, which in many respects are to be strictly classified with the alkaloid poisons, and which, like them, have no local effects, or at most very slight ones, but on the contrary general specific, or at least not limited, action.

Owing to the impossibility of classifying the glycosides from a chemical point of view, they must be divided according to their physiological effects.

The Glycosides of Digitalis Purpurea, Sea-Onion, and the Green Sneezewort.

The plants here to be considered act on the heart alone and in a specific manner, cause slowing of the pulse and increase of blood-pressure, and cause death by stoppage of the heart. Besides, they paralyze the striped muscles of the body. They can therefore appropriately be called "heart-poisons." They produce neither disturbance of consciousness nor convulsions, at least not by direct influence on the brain or the spinal cord. If unconsciousness and convulsions supervene shortly before death, they are due only to carbonic-acid poisoning from cardiac paralysis. The reason why all these heart-poisons cause vomiting has not yet been clearly explained. Many other poisons, indeed, powerfully affect the functions of the heart, for example alcohol, chloroform, and the allied substances (veratrine, etc.); but all these substances act upon nearly all of the other organs, such as the brain, the spinal cord, the respiratory apparatus, and the intestines, as powerfully as they do upon the heart, and cannot, therefore, be properly treated as heart-poisons.

All poisons whose action is confined to the heart-apparatus are embraced in the glycosides.

According to a classification by Husemann, such glyco-

cides are the following plants and plant families: First in importance the species of the scrophularinea called digitalis purpurea, with its three heart-poisons, digitalin, digitaleïn, digitoxin; then come the hellebores of the family ranuncaleæ (helleborus viridis, helleborus niger, and helleborus fœtidus), and the sea-onion (scilla maritima) of the family liliacea, the most important being scillaïn, which resembles digitaline. The apocynea have numerous glycoside-like heart-poisons: tanghicin, among the tanghinia venenifera, thevetin and its chemical product theveresine, of the thevetia neriifolia; finally strophantin, the African arrow-poison, iné (onage or kombe), of the strophantus hispidus. This last is perhaps also present in the oleander (nerium oleander), in apocynum cannabium, and in our evergreen (vinca major). Among the artocarpea, by far the most important is the arrow-poison of the poison tree of Macassar (antiaris toxicaria), together with its poisonous glycoside, antiarin. The Smilacea, in our Maybells (convallaria majalis) yield, besides the violent laxative glycocide convallarin, the heart-poison convallamarin.

The glycosides to be specially considered as of highest physiological as well as therapeutic importance in their action on the heart are the digitalis purpurea, the sea-onion, adonis vernalis, and the green sneezewort.

Folia Digitalis Purpurea and their Active Glycosides.

The plant digitalis purpurea (scrophularineæ), with its splendid red thimble-shaped flower, contains a large number of compounds which differ in chemical constitution but are similar in physiological action. They were originally denominated soluble (Walz), insoluble, non-crystallizable (Homolle and Quevenne), and crystallizable digitalin (Nativelle).

Schmiedeberg, however, proved that these various digitalins are not pure chemical substances, but are aggregations of many substances, partly perfect compounds in the plant and partly the chemical products of the plant's decomposition. According to him, the following may be regarded as genuine pharmacopic substances: 1. Digitonin, $C_{21}H_{32}O_{17}$, a glycoside which both in chemical and physiological nature is closely allied to the saponites (saponin); 2. Digitalin, $C_5H_8O_2$, insoluble in water; 3. Digitaleïn, which is distinguished from the preceding chiefly by its ready solubility in water, and which unites in a peculiar manner the properties of both digitonin and digitalin; 4. Digitoxin, $C_{21}H_{32}O_7$, the strongest of all in action. These four substances, together with their products (toxiresin, from digitoxin, digitaliresin, from digitalin, etc.), stand for all of the digitalin compounds above referred to.

PHYSIOLOGICAL EFFECTS.

(A) *The Individual Chemically Pure Digitalis Constituents.*

1. Digitoxin acts, according to Schmiedeberg, the same as saponin, and we have found his observations to be correct.

2. Digitoxin, digitalin, and digitaleïn, according to Hoppe, act with one another as does the mother-plant, therefore closely resembling the digitalis leaves in action. The strongest poison is digitoxin; it acts 6 to 10 times more powerfully than the other two; 1 kilo cat was killed by 0.0004 gramme, 1 kilo dog by 0.0017 gramme, and 1 kilo rabbit by 0.0035 gramme. In man 0.002 gramme cause very dangerous symptoms, lasting for several days, from which we conclude that man is less able to resist the influence of digitoxin than even the cat.

While digitalin and digitaleïn have no *local* effects, digitoxin, when injected subcutaneously, produces phlegmonous inflammation, with consequent suppuration. Another local effect seems to be produced by digitoxin, vomiting and diarrhœa following its employment; both symptoms cannot be of central origin.

All these substances act upon the heart in the same well-defined, peculiar manner as digitalis. First there is a rise in blood-pressure and a decrease in the frequency of the pulsations, then a falling of blood-pressure and at least in tests of blood-pressure—an increase in the frequency of pulsations. Dogs show the same symptoms as man.

The *voluntary muscles* in all animals, and also in man, are directly paralyzed; digitoxin effects this more completely than do the others.

On the other hand, the central nervous system and respiration are not affected, or at most are affected indirectly by the heart and the circulation of the blood; the breathing, also, by muscular paralysis.

The cause of death, apparently, is paralysis of the heart.

3. Of the chemical products of the various digitalis and old digitalin substances, toxeresin and digitaleresin have been accurately tested physiologically and found to be very similar, only the last-named being weaker in action (Perrier). Like picrotoxin, both excite the central nervous apparatus in the spinal cord and thus give rise to clonic *and tonic spasms.*

Reflex excitability is increased immediately after use, and decreases slightly until the spasm comes on. During the spasm reflex excitability again increases, but is soon completely paralyzed. The striped muscles are deprived of their excitability. The respiratory movements are hastened, the pulse, however, becoming slower and weaker; often the action of the heart is suspended, on account of paralysis of the heart-muscle.

Animals succumb to asphyxia and paralysis.

What becomes of the pure digitalis compounds in the organism is not known; Dragendorff, however, discovered traces in the urine.

In view of the fact that the digitalis leaves are used therapeutically only because of their action on the heart, it is highly desirable that of its various compounds which have heart-action, we should fix on one or the other, either digitoxin or digitalin, for exclusive use, and thus, by doing away with the mother-plant, eliminate the paralyzing digitonin and the tetanic toxiresin and digitaliresin.

Unhappily, Schmiedeberg was unable to predict a very useful future for the employment of the pure constituents of digitalis at the sick-bed. According to him, digitoxin is oftenest practically valuable; since when given in very small quantities (0.001 gramme) it produces the characteristic digitalis effects, and, though not abundant in the plant, can be separated comparatively pure. But since it is absolutely insoluble in water, and as the doses to be administered in medicine are so extremely small, great irregularity is necessarily the result on the functions of absorption, so that it is almost impossible to definitely estimate its strength of action. Digitoxin is also accompanied by the disagreeable local complication of vomiting. Digitalin and digitalein would be better adapted for practical use, since the desired effect is produced on the heart without any disturbing local consequences; but it is so difficult to obtain either of these in a state of purity that they should not be employed in the majority of cases.

The various impure digitalis substances put up by the trade cannot be recommended, on account of their changeable and indefinite constitution.

Thus we come to the conclusion that the mother-plant, at least for the present, should take the place of all known pure digitalis substances. We therefore proceed to consider the physiological effects of

(B) *The Digitalis Leaves.*

The active constituents of digitalis are absorbed by all mucous membranes, though the absorption is comparatively slow. We cannot, however, believe that they can permeate the uninjured skin.

Digitalis affects the heart of every animal poisonously, paralyzing it. The organ first destroyed by it is always the heart; after it is paralyzed the respiratory organs come to a standstill.

The reason why frogs retain life longer than warm-blooded animals is because they can generally exist for a time without either heart-action or blood-circulation.

Among warm-blooded animals, the carnivora and man are most sensitive to digitalis.

Digitalis has a cumulative effect; that is, after small doses have acted for a time, the general condition seems to be as though large doses had been administered.

We shall now describe *the symptoms and the functional disturbances of the single organs.*

The brain and spinal cord and their functions are not disturbed by medicinal doses, and only after long action and by large doses the following secondary results, due to feeble circulation and accumulation of carbonic acid, supervene: faintness, headache, prosopalgia, numbness, dimness of the sight, expansion of the pupils, illusions, syncope. The final convulsions of warm-blooded animals, are caused by carbonic-acid poisoning, in consequence of the arrested circulation. In frogs the same secondary causes of reflex excitability of the spinal cord are noticeable.

The Muscles.—The elongation of the muscular curve, which Weyland asserts is produced by digitalin, is denied by Evers; according to Koppe, digitalis has a paralyzing effect on all the striped muscles of the body. In frogs, digitalis causes extension of the muscles and increase of elasticity, both being due to a change in the condition of the contractile substance (Rossbach and Anrep).

Heart, Circulation, and Temperature.—Healthy persons, as well as those suffering from fevers and heart-affections, and similarly mammals (dogs), upon taking digitalis into the system, either by swallowing or subcutaneous injection, show the three following effects as stadia of its action on the circulation and temperature (Traube, Ackermann, Böhm), these effects in regard to duration and violence often hav-

ing numerous individual variations. After small doses of digitalis the first stage alone is noticed; after large doses the first stage is short and very imperfect, the second is longer; after deadly doses the third stage supervenes very swiftly.

1st stage: Very great slowing of the pulse, in consequence of violent excitation of the check vagus apparatus in the brain and heart; coincident with *great increase of the arterial blood-pressure* and contraction of the peripheral arteries, especially those in the cavity of the stomach, a consequence of irritation partly of the vaso-motor centre, partly of the peripheral nervous vascular apparatus; perhaps, also, a consequence of violent contractions of the heart and its resultant powerful action.

2d stage: Sudden and rapid acceleration of the pulse, in consequence of the paralysis, during the first stadium, of the irritated check apparatus of the heart: perhaps, also, in part a consequence of irritation of the nerves affected by the rapidly moving heart.

Blood-pressure gradually sinks during the frequent changes, in consequence of approaching cardiac debility.

3d stage: Extremely irregular heart-beats (arythm), but a constant decrease are perceptible; not, however, as in the first stage, in consequence of vagus excitation, but of weakness of the cardiac motor nerves and muscle.

Blood-pressure constantly falls; at last the heart remains paralyzed in diastole and cannot be caused to contract even by most powerful irritation.

Highly interesting are the actions of digitalis on the heart of the frog (Dibkowsky and Pelikan, Meyer, Fothergill, Böhm, Schmiedeberg), especially of the rana temporaria and, though less so, the r. esculenta. Very small doses cause powerful contractions of the heart; larger doses at first cause the heart to beat irregularly, the beat being not uniform but wavelike (peristaltic), and then produce so perfect a systolic condition that the ventricular spaces are completely obliterated by the approximation of the inner walls. The auricles, which continue their movements longer than the ventricles become, when not admitting the flow of blood, intermediate between the diastolic and the systolic condition. This systolic cessation of the heart through the effects of digitalis and the other powerful glycoside heart-poisons becomes more marked by the action of paralyzing and debilitating drugs such as prussic acid,

saponin, apomorphin, etc.; it is also made more apparent after long-continued evacuation of blood from the heart and finally by over-supply, which causes the heart to act more powerfully. Schmiedeberg combats the opinion (and he is in the right) that the above-described systolic cessation of the heart is a tetanic spasm of the muscle of the heart, since the tendency to the greatest possible degree of contraction is peculiar to the paralyzed muscles of the ventricles; all indications, he says, are rather against this idea, for it is probable that the influence of digitalis is to make the muscles more elastic without decreasing their perfect action, and that with the increase of elasticity the independent recovery of the muscles of the heart in disastole is constantly impeded.

We must guard against drawing conclusions to apply to warm-blooded animals from the action on the frog's heart; digitalis acts very differently on the two.

The *temperature*, in the first stage or after small doses of digitalis, decreases in the interior of the body and increases on the surface, because, in consequence of the increased arterial pressure, the movement of the blood near the skin is hastened, and therefore a rapid and general radiation of heat and a cooling of the interior takes place (Ackermann). The decrease of temperature in the subsequent stadia and during fevers has not yet been explained.

Digestive Organs.—Very small doses produce no results deserving mention. Patients suffering from severe cardiac debility and impaired digestion have their digestion improved as a consequence of the favorable influence of the circulation, the increased blood-pressure, and the more copious secretion of the digestive juices.

If small doses are continued for too great a time (0.001 grm. of the old digitalin daily, for eighteen days), bitter taste and nausea are complained of on the fifth day, loss of appetite on the twelth day, and from then on the hard excrements are voided less often (Stadion).

Medium and large doses (0.1 to 0.3 of the leaves, 0.005 of the old digitalin, 0.02 of digitoxin) cause dryness in the œsophagus, nausea, vomiting, eructations, long-continued loss of appetite, abdominal rumbling and pains, occasionally diarrhœa.

The last symptoms also occur if digitalis is injected *directly* into the blood; many observers assert that they *have noticed* inflammation in the stomach and intestine,

and Nasse observed contraction of the intestine produced by digitalis.

Urine.—Healthy men when dosed for days together with small quantities of the poison show no increase in the amount of urine or its constituents. When traces of general poisoning appear, the amount of urine discharged is somewhat smaller, as are also the specific gravity and the quantities of urea and phosphorus, sulphur, and chloride of sodium; only the uric acid is increased (Stadion, Mégeraud), and larger doses do not cause an increase in the discharge of urine in healthy persons.

Persons with heart-affections, especially with dropsical effusions, however, when given digitalis, discharge urine much more plentifully, but the digitalis does not affect them any more than healthy persons; not by an irritation of the parenchyma of the kidneys, but acts in the following manner: In most of these patients a watery transudation from the blood, owing to the immoderate venous engorgement, occurs. Digitalis regulates the engorgement and promotes reabsorption of the serous exudates. Thus the blood becomes watery and, as the pressure is increased in the venal arteries, more urine is excreted.

The *tissue metamorphosis* is wholly dependent on the action of the circulation; as long as the blood-pressure increases, more urea and carbonic acid are excreted; when the blood-pressure falls, these excretions cease (von Boeck).

THERAPEUTIC APPLICATIONS.

Digitalis has no just claim to the extensive therapeutic employment which has gradually been given it since it was first used by Withering in the last century for dropsies, for in most cases, especially in feverish conditions, it can and must be substituted by more reliable remedies. Nevertheless it is one of our most useful medicinal substances, and *for many heart-complaints an invaluable and often the sole remedy.* We therefore consider the uses to which it is to be limited.

The value of digitalis in heart-diseases was demonstrated at the beginning of this century (Kreyssig). Nevertheless we must consider its particular uses with extreme care, for there are cases in which digitalis is not only inefficacious but also hurtful. Digitalis is the main remedy for affections of the heart-muscle, for weakness of this muscle, and for

the disturbances thence resulting. This happens most often in valvular affections; but even here digitalis must not at all times be used without due caution.

It is contraindicated, first, in complete compensation, when organic valvular affection is balanced (compensated) by hypertrophy of the corresponding ventricle. Secondly, it is often contraindicated when valuvlar insufficiency has been newly developed (as may be in acute rheumatism) and the compensatory hypertrophy of the ventricle is but beginning; here other remedies are generally to be resorted to. Thirdly, whenever compensation is disturbed by dropsy, cyanosis or dyspnœa, and an abnormally high tension of arterial circulation, no matter from what cause. If digitalis, which increases pressure, is given under these circumstances, a hemorrhage of the brain may follow (Traube).

The use of digitalis is indicated when, in the stage of almost complete compensatory hypertrophy, there is strong action of the heart with very frequent, sometimes intermittent pulse, strong palpitation, and increased dyspnœa—a condition which often prevails after psychical and physical excitement. Its favorable action is best seen, however, in the stage of incomplete compensation, when the disturbances from the failure of the muscle of the heart, and, as a consequence of this failure, general dropsy, decreased diuresis, high dyspnœa, anorexia, and a frequent and irregular pulse, appear, with accompanying decrease in the volume and the tension of the arteries. All of these symptoms sometimes are dissipated with surprising rapidity. Yet one must carefully guard against administering digitalis for too long a time, for the contrary effect can easily be brought to pass. Moreover, it is advisable, when the good effect has been clearly produced, to discontinue the remedy from time to time. If, finally, the disturbance of compensation is due to the sudden increase of a resistance, as bronchial catarrh, the proper treatment for this must first be instituted; but in such cases, also, digitalis used in connection with the necessary remedies has been found useful. If digitalis is employed under the circumstances just mentioned, it is evident of what variety, anatomically considered, the cardiac defect is. A perfect diagnosis is required, since English writers (Corrigan, Sidney Ringer) assert that, for valvular lesions of the aorta, the remedy must be used very cau*tiously or not* at all. Experience contradicts this decidedly. *In valvular* lesions small doses should be given at first

(0.03 to at most 0.005 pro dosi, 2 to 3 hours), for reasons already made clear in considering the physiological action of the drug. If, however, these small doses are not effective, greater ones can and should be given, 0.1 and even more; a favorable influence will generally be obtained on the disturbed muscular activity of the heart.

It is clear that digitalis is also to be given, and in the same amount, in those cases where, without affections of the valves being present, the consequences of a weakness of the heart-muscle appear. These cases may occur in so-called idiopathic hypertrophy of the heart as a result of overtaxation of the heart, and also in myocarditis, if primary or secondary for example, pericarditis, etc. The use of the remedy is particularly to be recommended in cases where signs of venous engorgement, dropsy, etc., accompany a recurrence of bronchial catarrh with enphysema. These last-named symptoms are directly due, in this case, to the failure of the hypertrophic right ventricle; and digitalis therefore here forms an important link in the cure. For palpitation of the heart not resulting from valvular lesion digitalis is useful as a palliative, if the palpitation is caused by so-called "nervous influences" as a consequence of psychical affections.

We include here *pericarditis*, for which, in acute cases, digitalis is an important remedy. Results are due, not so much to action on the fever as to influence on the movement of the heart; by quieting this it is sought to influence the inflammatory process favorably.

Digitalis is much lauded as a diuretic. We have already mentioned that it is valuable as such by raising the aortic pressure. From this it follows that we cannot expect anything from its diuretic properties in cases of dropsy when the tension in the system of the aorta is normal or above normal, as we may see, for example, in chronic nephritis. On the other hand, it is always a reliable diuretic when dropsy can be traced to a failure of the heart, particularly in valvular lesions; and also, to a certain extent, when anasarca appears in patients subject to chronic bronchial catarrh and secondary hypertrophy of the right ventricle; this last supervening when the compensation thus established begins to be insufficient, in consequence of decreased strength of the right ventricle—symptoms which follow close upon one another in heart-complaints. The remedy is of little value for dropsy caused by simple hydræmia.

In acute fevers and inflammatory diseases digitalis has been used by Currie, Kreyssig, and to a much more general extent by the "contrastimulists," Rasori, Brera. At present it is going more and more out of use, for good reasons; we are now acquainted with highly energetic and reliable antipyretics (cold baths, quinine, salicylic acid); and, besides, digitalis lowers the temperature very gradually, and occasionally other highly unfavorable symptoms attend. Ten and twenty years ago croupous pneumonia was generally treated with digitalis. To-day we know that even more difficult cases, when not complicated, result favorably under expectant treatment. The duration of the disease is not shortened by digitalis; the danger of a fatal result, threatened by immoderate rise in temperature and increase in the frequency of the pulse, cannot be prevented by the action of digitalis, and an influence on the anatomic process is not to be looked for. All experience teaches that the influence of digitalis in pneumonia is only to affect the principal fever-symptoms, being chiefly on the pulse and, though to a less extent, on the temperature. Consequently its employment in this disease is advisable when there is a high temperature and a frequent pulse; but these fever-symptoms are controlled more readily and safely by other antipyretics, and the use of digitalis is consequently superfluous.

In *abdominal typhus* digitalis has been very often employed by Reil, J. Frank, and earlier physicians, and its very limited value was demonstrated. Their experience has been confirmed by that of more recent observers. In simple cases digitalis is superfluous; and as, by continued use, the digestion is injuriously influenced, as slight cumulative action may follow, and as, finally, we have remedies safer than digitalis which produce no bad after-results, it can be dispensed with in the treatment of typhus. If used at all, it should be with quinine, and only in cases of very stubborn fever in strong patients (Liebermeister). The value of digitalis in acute rheumatism, erysipelas, and pleuritis is to be determined by circumstances. It may be added that earlier physicians, as Goelis, Formey, and others, used digitalis for meningitis under certain conditions; experience, however, teaches us hardly ever to expect real good from its employment.

Should the remedy be given, the doses must differ somewhat in the kinds of fever and the stage: in general, medium doses are given, somewhat smaller for cases that last a considerable period (typhus), somewhat larger for those lasting a shorter

time; larger doses at the height of the disease, when a great resistance is generally offered to the action of the remedy (3.0 to 5.0 : 200), and smaller in the later stadia (1.5 to 2.0 : 200).

There remain a great number of other cases for which digitalis was formerly used or has lately been recommended. Observations prove, however, that in all it can be entirely dispensed with, or replaced by other more appropriate drugs. Only the most important of these affections need be named. First, phthisis of the lungs. Digitalis can be efficacious only in one form of phthisis, namely, the subacute feverish caseous pneumonia, and in this only by acting to decrease the temperature and the frequency of the pulse; but whoever has observed this variety of fever will hardly look for results from digitalis, even leaving out of consideration the fact that it impairs the appetite. Its use is also entirely superfluous in hæmoptysis.

According to Jones, who first used digitalis for *delirium tremens*, it has a very good effect on this disease; English and Swedish observers have partially supported this view. It is difficult to determine, from the information before us under what peculiar circumstances digitalis is peculiarly efficacious and deserves preference over other remedies. According to Fothergill, it should be employed when the action of the heart is weak and the pulse slow and irregular. In any case, the treatment of delirium tremens by digitalis cannot be determined by method, but must be decided by circumstances.

Dosage and Preparations.—1. *Folia digitalis.*—It has been shown above that digitalis is a remedy having decidedly cumulative action, and in whose employment very great caution is necessary, as well in giving small as in giving large doses. A patient treated with it must be seen daily, or better, if possible, twice a day. As soon as its effects are apparent (noticeable decrease in the frequency of the pulse or irregular beating of the heart), the use of the remedy must be suspended. If it is necessary to administer it for a considerable time (in heart-diseases), it is advisable always after a few days to intermit its use for a short period. We have already indicated in what cases digitalis must be used in small doses and in what cases larger doses must be given. The larger dose is 0.1 to 0.3 (ad 0.3 pro dosi ! ad 1.0 pro die !). The small dose is 0.03 to 0.05. Preferably in powders, or also in infusions. To children only in infusion, 0.05 to 0.05 : 120.0. The employment of the glycoside is not recommendable, according to what has been said in the physiological part.

2. *Extractum digitalis*, of very thick consistency, dark brown, when dissolved in water yellowish brown. Internally, 0.03 to 0.2 (ad 0.2 pro

dosi ! ad 0.8 pro die !). in pills or solution; for children, 0.003 to 0.05 pro dosi.

3. *Unguentum digitalis*, 1 part extr. d. in 9 parts ung. cereum. Externally. Entirely superfluous.

4. *Acetum digitalis*, 10 to 30 drops; useful, since it affects the digestion very little.

5. *Tinctura digitalis*, 5 parts fol. dig. in 6 parts spiritus. Of a brownish-green color, 10 to 30 drops (ad 2.0 pro dosi ! ad 5.0 pro die !).

6. *Tinctura digitalis ætherea*, 1 part fol. dig. in 10 parts spiritus ætherеus. Of a greenish color; 5 to 15 drops (ad 1.0 pro dosi ! ad 3.0 pro die !)

Treatment of Poisoning by Digitalis.—Dangerous poisoning seldom supervenes from accidentally taking large quantities; in cases of danger the stomach must be emptied by the usual methods and tannin administered. If the symptoms of absorption, as those shown by the circulatory apparatus, supervene, symptomatic methods may be adopted in the absence of physiological antidotes for digitalis, i.e., stimulants may be given in treatment of the collapse.

Squills—Bulbus Scillæ.

Squills (bulbus s. radix scillæ) of the urginea scilla (liliaceæ) contains a glycoside free from nitrogen, *scillaïne*, which Jarmested produced as a light, pulverizable, colorless or faint yellowish substance. It has a bitter taste, and is but slightly soluble in water, though freely so in alcohol. The substances sold as scillitine are not pure, but only extracts having widely different action. Squills, furthermore, contain considerable oxalate of lime (5 to 10 per cent), sugar, and vegetable mucus.

Physiological Effects.—The fresh squills act very powerfully on the skin and mucous membranes, so that at first deep redness and even vesicles are produced in the stomach and intestines.

Scillaïne acts, in general, on both warm- and cold-blooded animals the same as digitaline, and in the intensity of its effect is equal to digitoxine. Vomiting, diarrhœa, a similar change in the power of the heart, paralysis of the muscles, etc., are produced the same as with digitoxine. The production of diuresis depends, as with digitaline, upon the same changes in the circulation of the blood. Whether a change in the central nervous system is wrought by scillaïne has not yet been determined. On the other hand, injections do not cause phlegmonous inflammation, as Koppe has always observed, from digitoxine, (Jarmested). A deadly dose for a 1-kilo animal is: for rabbits, 0.0025; for cats, 0.002; for dogs, 0.001 grm.

Therapeutic Applications.—Scilla has, since ancient times, been employed as a diuretic, and partially with good cause. We have tolerably often been convinced of its good action; the second day of use the discharge of urine increases as much as 300 to 400 c.c. It has also been given in dropsies; the precise conditions, however, under which a good effect is to be looked for have not yet been sharply outlined; according to the observations of Husemann, they must be the same as with digitalis. Experience warns us to avoid scilla when any inflammatory condition of the parenchyma of the kidneys is present, and above all in acute nephritis. Its value for anæmic and cachectic dropsy is, as yet, undetermined.

In case of dropsy which develops in heart-disease when in a condition

of disturbed compensation, less benefit is to be expected than from digitalis; nevertheless a combination of both remedies is often very advantageous.

The use of the sea-onion requires a normal condition of the digestive organs. Experience teaches, moreover, that it is useless to look for the diuretic effect if the remedy causes diarrhœa from the beginning. Then it is evident that the application must not be continued too long even when digestion remains normal, because either the diarrhœa decreases or else an abnormal discharge of urine ensues; and, as we are convinced, the old symptoms return after a lapse of several days, or symptoms of affection of the kidneys appear which compel us to desist from the use of the drug.

S. is also used as an expectorant; that it is really of use for that purpose has not been proved. Besides, it is used as an emetic; but as we know of other remedies for this purpose that are decidedly more reliable, we can readily do without it. In fact, it is only used in combination with other emetics for children.

Doses and Preparations.—1. *Bulbus scillæ*, 0.02 to 0.2 pro dosi in infus., decoct., and in pills. 2. *Acetum scilliticum*, 1 part b. sc., 9 parts acetum, 1 part spiritus; a yellow clear fluid. Internally to 1.0 to 5.0 pro dosi, generally in mixtures or saturations. In using the latter the quantity of *acet. scillit.* should be cautiously measured and a carbonated salt added to complete saturation. 3. *Oxymel scilliticum*, 1 part acetum sc., 2 parts honey; yellowish brown, clear; taste, sour and bitter; 5.0 to 10.0 alone or as an addition to other mixtures; it is especially used as an emetic for children. 4. *Tinctura scillæ*, light yellow, 10 to 20 drops pure, or as an addition to mixtures. 5. *Tinctura scillæ kalina*, 8 parts bulbus scillæ, 1 part kali causticum, 50 parts spiritus dilutus. 6. *Extractum scillæ*, yellowish powder; 0.02 to 0.2 pro dosi, in solution.

Adonis vernalis, a ranunculacea, acts similarly to digitalis, and is said to have restored the action of the heart in cases of disturbance of compensation, and also regulated its action when digitalis no longer had any effect (Bubnow). Adonis appears, therefore, to be a good substitute for digitalis, and it is advisable to use it to replace digitalis after that has been used for some time, the more so as its effects are not cumulative, and it can be given in large doses (3.0 to 7.0 : 150.0). Nevertheless we (Nothnagel) have not seen any mentionable or clearly proved result in cases of heart-disease when a disturbance of compensation prevailed.

Green sneezewort, radix hellebori viridis.—The roots of the helleborus viridis and of the helleborus niger (ranunculaceæ), according to Husemann and Marmé, contain two glycosides, helleborein and helleborine.

Helleborëine is a strong cardiac poison, and acts like digitoxin on the skin, mucous membranes and the heart. *Helleborine* acts much less on the heart, but is very stupefying and anæsthetizing. Therapeutically it is quite superfluous. Radix hellebori viridis ad 0.3 pro dosia! ad 1.0 pro die!

THE GLYCOSIDE OF SENEGA AND SOAP-ROOT.

SAPONINE.

The senega-root of polygala senega (polygaleæ) contains an active ingredient, the glycoside saponine, $C_{32}H_{54}O_{18}$ (?), a colorless amorphous powder which dissolves in water into a foaming liquid, and through addition of muriatic acid becomes resolved into an uncrystallized sugar and sapogenine, $C_{14}H_{22}O_4$.

PHYSIOLOGICAL ACTION.

Saponine.—It tastes rather sweet at first, afterwards a sort of stinging bitter; when inhaled it causes sneezing. It produces abcesses at the site of hypodermic injection. According to Pelikan and H. Köhler a 5-per-cent solution injected under the skin of a frog primarily paralyzes the contiguous sensitive and motor nerves, eventually killing them. Thus the spinal cord is paralyzed. If, on the other hand, the spinal cord is brought under the influence of saponine first, then after tonic spasm has ensued, central paralysis appears first and gradually advances to the periphery. All the muscles of the body also become paralyzed, the striped ones of the extremities and the heart-muscle, as well as the smooth intestinal muscles, so that its introduction into the stomach rapidly causes the muscular coat of the stomach and bowels to lose its sensibility, and the heart ceases to beat, being paralyzed in diastole. At the spot of injection the capillaries (and according to circumstances the larger arterial trunks also) contract and a local stasis of the circulation consequently results. In warm-blooded animals also, the muscles of the body and the peripheral nerves become paralyzed—especially those which are nearest to the spot where the injection has been made. About the heart the retarding as well as the accelerating nerves, and the muscles of the heart, become paralyzed, and at the same time blood-pressure, temperature, and respiration fall. When saponine is not injected under the skin or into the blood, but is introduced into the stomach, no paralysis of the peripheral sensory and motor nerves, nor of the striped muscles, ensues. Schroff noticed after giving saponine: inclination to cough and increased secretion of mucus in the respiratory tract, and no increase of perspiration or of urine. The fact that Schroff did not observe symptoms of severe poisoning after internal doses of 0.2 grm. to human beings may have been caused by its small degree of diffusibility, and possibly also by its difficulty of solution in the digestive juices. If such a dose had been injected under the skin, according to the experiments made by Keppler on himself, death must have inevitably followed from brain and heart paralysis, as a *single dose of* 0.1 grm. caused the appearance of a violent *erysipelatous* inflammation at the site of injection, with fear-

ful pains in the left side of the head, eye, and extremities; extraordinary bodily and mental depression; eventually an extraordinary fall of the temperature; and produced a sickness of five days, during which the patient was brought to the very verge of the grave.

Senega-root.—This has a sharp, bitter taste; given in small doses (0.3 to 0.5 grammes) hourly it causes no diminution of appetite, but a small decrease in the heart-beats, inclination to cough, and mucous expectoration (Böcker). We record the statements that the quantity of urine, and in it the urea, the uric acid, the phosphates, and besides all this the exhalation of carbonic acid, are increased, without being able to substantiate the same on account of imperfect methods of experiment. Large doses (1.0 grm.) of senega-root given every two hours cause increased flow of saliva, burning in the stomach, sensations of strangulation, vomiting, and liquid stools. The skin becomes warm and moist; the urine is increased (Sundelin).

THERAPEUTIC APPLICATION.

Senega is used only as an expectorant now. Its use is entirely empirical, as follows: Senega is considered an expectorant when secretions are accumulated in the bronchiæ, which is manifested by muco-purulent expectoration. Auscultation shows this condition to correspond with the presence of (so-called moist) rattling râles. The removal of these free secretions from the bronchiæ is materially assisted by senega. It would therefore be efficacious in the second stage of acute bronchial catarrh, also in chronic bronchial catarrhs, again in bronchial blennorrhœa; it can also be used to advantage in pneumonia when, after the fever has abated, in the stage of resolution, there are signs of copious bronchial secretion. Another condition for its use is a normal condition of the digestive apparatus, especially a good appetite. While small doses do not impair digestion, they nevertheless act unfavorably when the patient is suffering from anorexia. Again, it is essential that the patient be free from fever, or at least the increase of temperature must be but slight. In these conditions we find that expectoration is facilitated, and good authorities, for instance Stokes, give senega the preference above all other remedies for this purpose. That the pathological process on the bronchial mucous membrane is influenced

by it is improbable; at all events, the subject has not been carefully studied. We call special attention to the fact that as the result of experience the use of senega must be avoided in phthisis. Physicians formerly gave senega in cases of pneumonia to a great extent, even whilst fever still existed, when expectoration stopped, in consequence, as they thought, of a "weak condition of the bronchiæ;" they were even not afraid in cases of pneumonia to treat fat, old, and phlegmatic patients with senega from the inception of the disease.

Saponine, for which Pelikan and Köhler claimed local anæsthetic powers, is proven to be beyond practical use by the clinical experiments of Eulenberg and Keppler. The pain at the place of injection is very acute, the subsequent anæsthesia very insignificant, and the general appearances are so unpleasant and even dangerous that in Keppler after 0.1 they lasted over six days, and this physician nearly paid for the experiment with his life. These dangers also prohibit Keppler's suggestion that saponine, on account of its energetic action in reducing temperature, may possibly be used as an antipyretic; just as veratrine could not be used for the same purpose.

Dosage and Preparations.—1. *Radix senegæ*, 0.3 to 0.5 pro dosi, in infus. or decoct.

2. *Extractum senegæ*, yellowish-brown powder; soluble in water, which it renders turbid; 0.3 to 0.5 pro dosi in pills.

3. *Syrupus senegæ*, by the teaspoonful alone, or as addition to expectorant mixtures.

4. *Saponine.* Internally, 0.03 to 0.1; subcutaneously, 0.01 to 0.03.

The following plants and ingredients contain saponine: soap-root, radix saponariæ, from saponaria officinalis (silaneæ)—this is very unnecessary, still officinal; also the root of gypsophila struthium and other silenes; the bark of quillaja saponaria (spiraeceæ) and the monesia bark of chrysophyllum glycyphlaeum (sapoteæ).

It is said that the smilacin from the root of sarsaparilla has similar effect to saponine, and the same is claimed for cyclamin in primula veris, and cyclamin europæum.

APPENDIX TO THE GLYCOSIDES.

The following matters are not applied therapeutically:

Picrotoxin, the very bitter effective ingredient of the cocculus seeds (semina cocculi of anamirta cocculus, minispermeæ), and *cicutoxin* (Böhm), the resinous effective ingredient of the water-hemlock (cicuta virosa). Both have an extraordinary resemblance in their physiological action.

In consequence of violent excitation of the medulla oblongata they produce peculiar convulsions, acceleration, and arrest of respiration, and

elevation of the blood-pressure; they also excite the vagus. The brain and spinal cord are not affected, or only secondarily.

Solanin, $C_{43}H_{71}NO_{16}$ (?), the glucoside alkaloid of several kinds of *solanum*, particularly of the bitter-sweet (stipites dulcimaræ), has a paralytic effect on the central nervous system of warm- and cold-blooded animals; therefore effects general paralysis, reduction of respiration and of the action of the heart, and kills warm-blooded animals with suffocative convulsions. Similar are the effects on human beings (Husemann, Schroff, Fronmüller), with whom nausea and vomiting ensue.

PROTEINE MATTERS.

Albumen and Peptone.

The albuminoid matters are essential components of the animal body, as well of the solid as of the fluid parts; they are only engendered in plants, and from them are taken up in the shape of food, directly by the herbivoræ, and indidirectly by the carnivoræ. Most of them are amorphous and contain carbon and nitrogen, hydrogen, oxygen, and sulphur, and in very similar conditions in the various albumens, so that we may almost ignore the difference that exists in the different albumens and consider them as incidental complications or mixtures. Therefore in the body of every animal any modification of the same can become changed into another modification, and one and the same food containing albumen is the source of all albumen modifications in the various tissues of the body.

Omitting a consideration of ash, the constituents of the various albumens vary within the following narrow limits:

Carbon	50	to 54	per cent.
Hydrogen	6	to 7	"
Nitrogen	12	to 18	"
Sulphur	0.4	to 1.7	"
Oxygen	20	to 26	"

As this table of percentage shows that to one atom of sulphur there are about three hundred of carbon and six hundred of oxygen, it follows that its molecules must be of enormous size and of exceedingly complicated structure, of which its various products of decomposition offer but a cursory suggestion.

Albumen must be considered among the most important articles of food and on a par with fat, the carbohydrates, salts, and water, without which no food can support life.

However, according to the condition of the body, these matters must be allowed to exert their influences in different forms and from different directions, and it behooves us to learn these therapeutic modifications; that is to say, to show, when the œsophagus is closed, under what conditions absorption of the albuminous bodies by the rectum is effected; also how to make their digestion possible in case of disease of the stomach, and so on. The study of nutrition will be discussed only in as far as is necessary for the clear understanding of the matters we are considering, as more than that would require extensive swerving from our plan.

The different albumens (egg, serum, vegetable albumen), and globulines (vitellin, myosine, fibrine), alkaline albuminates (caseine), we never consume pure, but contained in meat, eggs, milk, cheese, blood, and so on, mixed with many other nutrient matters; wherefore we shall consider them only in their natural combinations. Besides, we must also consider an albuminoid ferment, pepsine, and the digested albuminous substance, peptone.

PHYSIOLOGICAL OBSERVATIONS.

Whilst pure albuminous substances are tasteless, on which account they do not call forth secretion of the digestive juices and are not easily digestible, they are, when found in their natural condition, combined with more or less salts, and thereby attain a high degree of digestibility. Human beings improve this by the addition of salt, vegetables, and by cooking.

Albumen is brought into a fit shape in the stomach for absorption, principally through the influence of the pepsine and of the hydrochloric acid of the gastric juices, which converts it into peptone (which means that it is digested). Peptone is more easily soluble in water, no longer coagulates at the boiling point, diffuses itself readily through animal membranes, and is, therefore, absorbed into the circulation with great celerity to the very last trace. After the belief had existed, for a long time, that peptone was no *more an* albumen, but only a product resulting from its de*composition, which* could not regenerate itself into albumen

in the organism (Tiedemann and Gmelin), and which was of small importance for the nourishment of the body, that it did not contribute to the building up of the tissues, and that it at once became urea in the blood (Brücke, Voit, Fick), Hermann assumed that though peptone certainly consisted of the products resulting from the decomposition of albumen, but which combined again in the system into complicated albuminous molecules.

Plosz and Maly proved, later, that the peptones furnish the same nutrient values for the body as albumen. Animals in whose food peptone was substituted for albumen, not only maintained their full weight, but thrived, and continued growing to their full strength. As albumen was totally omitted from their food, the animals could have no other source but peptone whence to draw the material to replace the loss incidental to tissue metamorphosis, as well as for the increase of the volume of tissues and organs in their growth. Animals fed first with albumen, and then with a like quantity of peptone, it was found that their condition was better in the latter than in the former instance. Adamkiewicz also proved that peptone is qualified to mix in with the juices, and to be elaborated by the cells, as albumen is, and that it affords material proper for the formation of cells and tissues.

What we represent to ourselves as peptone is not clearly demonstrated in the most recent works; but it is evident from comparative analyses of albuminates and peptones, that peptone cannot be a product of decomposition, but that albumenates and peptonates must be regarded as isomers of the same substance (Lehmann, Thiry, Kühne, Maly). Kessel confirms the opinion previously expressed that the albuminous molecule loses carbon and nitrogen during pepsin digestion, and that it then experiences hydation, or oxidation. Herth assumes that the albumen molecule, in its conversion into peptone, only experiences an internal transposition, or, so to say, a reciprocal displacement of its elementary components, which change either in the blood, or in the tissues readily reconstruct into the albumen molecules.

The digestion of the albumen which has not been digested in the stomach is continued in the intestine by the pancreatic juice. But it appears that not only new peptonoid substances are formed there, but that further and more profound divisions of the albuminous molecule occur.

Albumen enters the blood, partly as such (Brücke), but *in greater part as peptone*, and then serves as much as a substitute for the consumed albuminous material of the cells, and also is subjected to further division, whilst groups of atoms containing nitrogen free themselves from those which do not; the former are chiefly leucine and tyrosine, which afterwards become urea (Schultzen and Nencki)—the latter possibly being the chief foundation of the fats, perhaps also of the liver-glycogen. In the blood the peptone, which has been taken up from the intestinal canal, disappears so quickly that it is difficult to find even a trace of it left, after ever so copious an absorption.

It must here be mentioned, that when undigested albumen (from the hen's egg) in solution is injected into the blood of an animal, invariable albuminuria ensues. Whether this albumen formed in the urine, is the same injected egg-albumen is not positively known; but an argument against this theory is that all experimenters found more albumen in the urine than they had injected into the blood,—serous albumen or peptone, when injected in the same manner; and which does not again appear in the urine, excepting when, in consequence of the injection, secondary disease of the kidneys has ensued.

The albumen which has been taken up by the cells, and which has been reconstructed from peptone, again is decomposed by the vital processes; but not nearly so rapidly as was formerly believed,—especially the researches of Fick and Wislicenus on the muscle cells have corroborated the view, first enunciated by M. Traube, that muscular action supplies the necessary vital force by the elimination of a non-nitrogenized part, whilst the nitrogenized group of atoms of the albuminous molecules manifests but traces of gradual destruction. When the quantity of albumen necessary to replace the daily excretion of nitrogen in an adult (18.3 grms.) is calculated, it is found that 118 grms. are required (Forster, Voit); and when the average amounts of albumen daily consumed in food by various people is taken, the result is 131 grms. (Voit).

The albuminous bodies consumed with food, considered briefly, have the following significations:

1. One single modification of albumen—for instance, caseine from milk—or the two albuminous modifications of *the albumen* of the hen's egg, can supply the organism *with all of its* albuminous modifications, which possibly are

thousand-fold, as every individually distinct group of cells presents differences in its albuminous bodies.

2. Besides this, gluten, mucus, and urea derive their origin from the albuminous bodies.

3. Furthermore, a great part of the fat, the glycogen, and some constituents of bile, are, in great part, derived from albumen.

It may therefore be safely said that all organs and tissues can only develop in the presence of albuminous bodies, and they form the most important cell substrata, without which the functions of the cells could not be performed.

Excretion.—Only very small quantities of albumen leave the body as such, in hair, nails, epithelial scales, mucus, semen; and in pathological cases, in pus and in albuminous urine. After exercising its functions, the greater part decomposes, as indicated above, into more simple bodies that are deoxidized as far as they can be.

The nitrogen of the albumen finally appears almost entirely in the urine as urea, uric acid, kreatin, kreatinine; the sulphur also appears in the urine as sulphuric acid, the hydrogen and carbon as water and carbonic acid, partly in the urine, partly in the exhaled air, and in the perspiration.

THERAPEUTIC AND DIETETIC USE OF THE ALBUMINATES.

From a clinical standpoint, it is necessary only to refer to the conditions in which the albuminous matters have to be given as principal nourishments, for, there can certainly never be any occasion for their exclusive ingestion; and we must also mention the conditions in which they must be avoided as much as possible.

A *copious ingestion of albuminous substances* must occur in those cases where the building up of the tissues is to be promoted. This is the case during the period of growth and development, i. e., in youth, and more especially during *early infancy;* again, with convalescents, either from acute and sub-acute febrile disorders or with those forms of chronic diseases accompanied by pathological exudations and emaciation. Meat, eggs, and milk: these are the real and essential agents used as invigorating treatment in such cases, against which—supposing appetite and digestion to be normal—all pharmaceutical preparations have to stand back, as they are entirely superfluous. It is not our

province to discuss the application of this method in detail. We will only mention that food should never be given in considerable quantities. The rule is this: Finely scraped raw or rare beef, ham, very finely chopped pigeon, or chicken-breast, the yolk of an egg in beef-broth, etc.; the various substances must be carefully selected in every particular case.

The same rules apply to the treatment of *anæmic conditions*, even if there be no emaciation by loss of muscular and adipose tissue, *e.g.*, acute anæmia after loss of blood, or accompanying chlorosis. In these cases there must be an additional exhibition of the chalybeates, as has been mentioned under the latter head.

We need but to allude to the necessity of putting cases of *diabetes mellitus* on a diet consisting principally or rather exclusively of albuminous (and fatty) substances; it is well known that we must avoid those which are rich in sugar and starch or dextrine (milk, cereals, etc).

For persons with a tendency to *obesity*, such a diet, consisting principally of albuminous matters, and as containing as little fat, hydrocarbons and gelatine as possible, is the most proper; to reduce a large deposit of adipose tissue, a method, based on this principle, has, in modern times, been developed by *Harvey*, and is well known under the name of Banting's treatment.

It must be borne in mind however, that, by adhesion to a strictly albuminous diet, very frequently digestion becomes disordered; to avoid this, it is commendable to order an occasional change of diet for several days.

One thousand years of practice have taught us to avoid albuminous substances during febrile states; the *diet of fever* was essentially fixed at the times of Hippocrates. And yet the rigorous and complete exclusion of albuminous matters from the diet of fever-patients has to-day been quite correctly dropped. It is true that we are not prepared to nourish a patient, severely sick with typhoid fever, by giving him a leg of mutton or a roasted hare; aside from all other reasons, for this simple one: that he would not be able to digest such substantial fare. But as we have recently learned that a fever-patient takes alcohol not only without detriment, but with direct benefit, contrary to the views formerly held, just so do we know that in all febrile diseases of longer than a week's duration, albuminous matters given in a proper, *i. e.*, in fluid form, do not at all in-

crease the temperature, but effectually help to preserve the system. Typhoid fever patients who take from one to two litres of milk, and from four to six yolks, stirred up in beef-broth, in the twenty-four hours, do not show any elevation of temperature from such diet; on the contrary, *ceteris paribus*, the emaciation is less marked and convalescense less protracted. The same is true for patients with hectic fever, phthisis, etc.

FOODS AND DRUGS THAT CONTAIN ALBUMINOUS SUBSTANCES.

The most important of these (meat, egg, and milk) contain, beside albumen, all the other ingredients necessary for the preservation of the body: gelatine, fat, sugar, mineral salts (q. v.), so that many animals do not require any other food.

Meat.—The muscular tissue of the mammalia, birds, and fish, used as food, has on the average the following composition, per 100 grms. (Moleschott):

	Mammalia. Grm.	Birds. Grm.	Fishes. Grm.
Soluble albumen and hæmatine	2.17	3.13	3.60
Insoluble albuminous matters and their derivatives	15.25	17.13	10.13
Glutenoid matters	3.16	1.40	4.39
Fat	3.71	1.95	4.59
Extractive matters	1.59	1.92	1.60
Kreatine	0.09	0.19	0.09
Mineral matter (salt, K, Na, Ca, Mg, Fe, P, S)	1.14	1.80	1.49
Water	72.87	72.98	74.08

Raw meat, at least if taken in large morsels, is less quickly digested than boiled or roast meat. For patients, the best suited is tender meat with very little fat, especially from wild herbivora, fowl; then beef and veal: much less digestible is pork, mutton and goose—flesh which have too much fat. Rare meat is of great value as a nutriment, and is the most palatable and most easily digestible. Boiling, and still more pickling, deprives meat of many of its nutritious ingredients, which are dissolved in the broth or sauce. (See beef-broth, bouillon.)

Solution of Meat.—The solution of meat (solutio carnis) first prepared by *Leube-Rosenthal* is made thus: 1000 grms. of beef, from which all fat and bones have been removed, is chopped, filled into an earthen,—or porcelain—pot, and 1000 ccms. of water and 20 grms. of pure hydrochloric acid added. This pot is placed in a *Papin's* pot and closely covered; it is then boiled for from 10 to 15 hours, being stirred occasionally during the first few hours. After this the mass is taken out of the pot and pounded in a mortar till it resembles an emulsion. Then it is again boiled for from 15 to 20 hours without opening the cover of the vessel (Papin's); then carbonate of potash is added until it is almost completely neutralized, and finally stewed to the consistency of paste. It is then divided in four parts (250 grms. of meat in each) and administered in broth.

This prepartion is well borne in gastric disturbances; firstly, because it resembles an emulsion and, then, because by this process the meat is subjected to conditions similar to those obtaining during the digestive process; consequently the activity of the stomach is taxed very little, and the preparation can be absorbed by the stomach without difficulty or pass on to the small intestine unchanged. (Leube.)

It is of great advantage, therefore, in all those cases in which the physiological action of the stomach is very low, or where it must be taxed as little as possible. This is the case largely during diseases of the stomach itself, especially in cases of simple gastric ulcer; but then also in the course of acute or chronic febrile diseases.

It is very unfortunate that, according to our experience at least, a decided unsurmountable disgust against its administration is soon developed, so that its exhibition must of necessity cease.

Enemata of Meat and Pancreas.—*Leube* orders 150 to 300 grms. of meat, chopped with a cleaver as finely as possible, together with 50 grms. of finely chopped pancreas of the ox and 100 to 150 grms. of lukewarm water, to be stirred and mixed to a pasty consistency and to be injected high up into the gut, which has been previously emptied by simple water. *Kunkel* advocates (correctly) the addition of a few drops of a solution of carbonate of soda to render the mixture somewhat alkaline and a little more common salt, because, according to *Voit* and *Bauer*, albuminous solutions are absorbed more readily by the large intestine when they contain common salt.

By the action of pancreatine the albumen is converted into peptone even in the alkaline intestinal solution, and consequently is for the most part taken up by the blood from the intestine.

These enemata may be used with great advantage in certain diseases of the stomach in which, as in gastric ulcer, no other nourishment is borne, or in those cases of stenoses in some portion of the gastro-intestinal tract where ingestion of sufficient quantities of food by the mouth is impossible. We are able to sustain life thereby for a certain time.

Beef-Broth, Bouillon.—Meat loses about 15 per cent of its weight by boiling, and the parts thus lost are dissolved in the water. In 100 grms. of broth there are contained about 1.5 grms. of organic matter (0.1 grm. gelatine, some kreatine, kreatinine and sarcosine) which are of little value as nutriments; 1.0 grm. of salts; in thoroughly boiled meat, only one fifth of its original percentage of salts.

Bouillon, beef-broth, on account of its agreeable taste is more frequently used because of this quality than taken as nutriment proper. It is, however, an excellent menstruum for really nutritious substances, especially yolks of eggs. The best broths and those most frequently used are those from chicken, beef and veal.

Cold Infusion of Beef.—The cold infusion of beef (infusum carnis frigide paratum Liebig) is prepared by macerating finely chopped meat with 0.1 per cent muriatic acid for from a half hour to an hour and then decanting. The addition of common salt must be avoided, because it precipitates a large part of the albumen that is held in solution.

It is an unsuitable preparation, because only a small percentage (1‡) of albumen is in solution.

Extract of Meat.—Liebig's extract of meat (extractum carnis Liebig) contains neither the albuminous matter nor the gelatine nor the fat, *i.e.*, *not the really nutritious constituents of meat, only its palatable extractive matter and salts.*

Analysis of the Extract of Meat (after Bunge):

Water	17.9
Ash	21.9
Organic constituents	60.2

Composition of the inorganic constituents (ash):

KO	46.12
NaO	10.45
MgO	1.96
CaO	0.23
Fe_2O_3	Traces
PO_5	36.04
Cl	6.39
SO_3 (proper)	0.27
	101.46
Minus the one equivalent of oxygen, combined with Cl	1.46
	100.00

Liebig's assertion that, by an addition of extract of meat to vegetable food, the full nutritious value of fresh meat can be attained, is disproved by *Voit* by means of his apparatus for respiration; also Liebig's other assertion—that the extractive matters of the muscle (kreatine and kreatinine are of some importance to those processes that take place in the apparatus which develops muscular power and represents the working material of the muscle—has also been disproved by *Meissner* and *Voit*, who were able to prove that both kreatine and kreatinine, when ingested, are excreted unchanged by the kidneys after twenty-four hours. The amount of nutritious salts contained in the extract of meat has no special importance, for the reason that a sufficient quantity of these salts is introduced by the ingestion of vegetable food.

The only value, therefore, of the meat extract is as a palatable food. That this use, however, is not to be despised we have already sufficiently shown upon several occasions; for example, in regard to alcohol.

Accordingly, nothing can be said in favor of its strict medical application as a material for an invigorating treatment; all that can be said is that practically it only performs the same office as fresh meat-broth. The latter has the advantage, to most persons, that its taste is more agreeable, but the meat extract has an advantage which is not to be underestimated, viz., that the preparation may be carried anywhere, may be always at hand, and will keep a long time. Its mode of use in the kitchen is generally understood. Kemmerich suggests 5 or at most 10 grammes as the quantity for daily use by adults.

Eggs.—Hens' eggs contain the same inorganic and organic elements as meat under similar proportions, only they contain less salt and are not as palatable.

With regard to their dietetic use, we refer to page 786. Frequently the whole egg is not employed, but merely the yolk, especially in the case of children suffering from atrophy, of persons recovering from typhoid fever, and others in a similar state. Hard-boiled eggs are the most dif-

ficult of digestion, unless they are reduced to very small particles before being eaten.

The only use of eggs by way of direct medical application worthy of mention is in cases of poisoning by corrosive substances. Furthermore, they are used in the preparation of various kinds of medicines, emulsions, liniments, and salves.

Blood.—Animal blood also contains all the nutritive elements and salts of meat, only it is much more difficult of digestion, so that a larger portion of it passes from the body with the fæces, and it possesses no advantage over meat. At the present day no use is made of it therapeutically.

Milk.—Milk (lac) of different species of animals has the following component parts (Gerup-Besarnez). It contains:

100 parts milk—	Woman's.	Cow's.	Goat's.
Water	88.9	85.7	86.4
Solids	11.1	14.3	13.6
Caseine	3.9	4.8	3.4
Albumen	—	0.6	1.3
Butter	2.6	4.3	4.3
Sugar of milk	4.4	4.0	4.0
Salts	0.1	0.5	0.6

It is therefore, like meat and eggs, a means of nutrition which contains all the elements necessary for the support of the body, and accordingly human beings, and especially children, are found to grow and thrive by the use of milk as the sole form of food.

The use of milk for medicinal purposes, aside from its value as the normal kind of food for children, is not very manifold. In various pathological processes it forms an almost indispensable kind of nutrition. In this class belongs, above all, its use in cases of pulmonary consumption.

In connection with kumys (q. v.) we have discussed the use of cod-liver oil, and shown that in cases of phthisis this form of nutrition can be resorted to only when certain special conditions exist. The same conditions are also requisite for milk when it is desired to make use of it by way of systematic cure. Even when these conditions prevail, it is necessary to wait for the epochs indicated with reference to the other substances before proceeding to a methodical milk-cure. Such cure must not be resorted to while the presence of a somewhat high and persistent fever continues and the course of the disease continues. Another necessary condition is that the appetite should be good, and that there should be no trouble with the digestion. We would here urge strenuously that this requisite is of importance, not only before introducing the milk-cure in phthisis, but also in all other diseases. The case is somewhat different when milk is administered in small quantities and not systematically in large quantities. Small quantities may not only be used without injury during the continuance of high fever, but are hardly surpassed in nutritive value by any other substance which may be digested with equal ease; it would be difficult to find any substitute for milk taken in this form.

The milk-cure may be resorted to in other forms of disease of the lungs of a consumptive character as well as in phthisis, as well as also in

bronchial blenorrhœas. It is also beneficial in connection with other necessary therapeutic measures where cachexy follows severe intermittents, severe, long-continued, acute febrile disorders (for example, typhus), profuse suppuration. In chlorosis surprising results are usually obtained by a systematic and continued use of milk-diet, more so sometimes than from an abundant supply of meat-food.

A long time ago, and then again of recent years, systematic milk-cure, to the exclusion of drugs and with the use of only very small quantities of other forms of nutrition, has been highly recommended in dropsy, and especially in *chronic nephritis*. It has been stated that with such exclusive milk-diet the dropsical symptoms disappear, the patient's difficulties are lessened, the processes of nutrition are improved, and, besides, the amount of albumen in the urine diminishes. Other observers, however, do not think that they have observed any greater improvement than by the use of other methods. The benefit of the treatment ought to be estimated according to the nutritive value of milk. Observations of exclusive milk-diet in *diabetes mellitus* have not as yet been sufficiently extensive to permit the formation of an accurate judgment of its benefits in such cases.

Beneficial use of a systematic milk-diet. to the exclusion of most other forms of nutrition, may be made in chronic disorders of the stomach, particularly in *ulcus ventriculi*. The object of the diet is by the use of milk, which with a few other substances suffices for the maintenance of life, to introduce into the stomach a kind of food that will irritate the walls and the surfaces of the ulcers as little as possible, so as to give the latter an opportunity to cicatrize. We would remark that in this class of cases, in order to prevent vomiting, the milk must frequently be taken cold, whereas in the classes previously mentioned it may be taken warm or lukewarm. An exclusive milk-diet is often successful in obstinate chronic catarrh of the stomach and even of the intestines, beginning with diarrhœa. In such cases it is often necessary to administer only very small quantities at first, a few tablespoonfuls at a time.

Milk, as a means of nutrition, requires next to be noticed in acute diseases of a febrile character and of long continuance, such as typhus, puerperal fever, etc. If there is diarrhœa, the milk must be boiled with some mucilaginous substance. Of course in such cases there is no question of a systematic milk-cure, but merely of the administration of small quantities.

Among the other modes of administering milk, its use in *poisonings with corrosive substances* requires separate mention. Its operation in them is twofold; that is to say, sometimes it stands in the relation of a direct antidote to them, as, in the case of corrosive metallic salts, the caseine contained in the milk forming a combination with them; and then it immediately forms a coating and protection on the corroded spots upon the mucous membrane.

In many cases in which milk is administered no positive result is expected from it as such, but only, inasmuch as it is taken warm, that it may serve as the vehicle of a more elevated temperature. To this class of cases belongs the treatment of children with *pseudo-croup*, which often manifests itself very suddenly at night, by giving them hot milk to drink. And in this category belongs also the administration of milk, generally mixed with Selters water, in bronchial catarrh.

Milk is also applied externally in various ways. Thus, in certain cases it is used, of course warmed, in place of a warm poultice; for example,

in many acute inflamed conditions of the cavities of the mouth and throat, of the *meatus auditorius externus;* in the first by way of gargle, and in the second, as an injection. Milk is also used for aperient clysters, in combination with honey or sugar, without, however, having a preference over camomile tea and water for the purpose.

Of the preparations of milk which are used for remedial purposes, special consideration will be given below to what are called wheys. Here we have a word only to say in regard to buttermilk. Sweet buttermilk is frequently used in the same manner as milk, without having any especial advantage over it; great care must be taken in the use of sour buttermilk, as it is apt to disorder the digestion and to cause diarrhœa.

Condensed milk is made by the evaporation of milk *in vacuo* with the addition of sugar of milk, and is used, mixed with 3 to 4 parts of water. It is found serviceable where no good fresh milk can be had.

Whey (erroneously called milk serum, *serum lactis*) is produced from cow's milk by the admixture of rennet or of some organic acid; its principal ingredients are the salts found in milk and the sugar of milk, and, likewise, also some small quantities of albumen and caseine. It is a greenish-white liquid, of a sweetish-salt taste. According to the investigations of J. Lehmann in Bad Kreuth, 1000 grammes of whey contain—

	(*a*) Of Goat's Milk.	(*b*) In the Whey obtained from this Milk.
Albuminous matters	27.78	5.81
Butter	38.38	0.20
Sugar of milk	42.47	49.69
Salts	7.43	6.65
Water	883.94	937.65
	1000.00	1000.00

Among the salts are found potash, natrium, lime, magnesia, phosphoric acid, sulphuric acid, chlorine, and carbonic acid, particularly in the form of chloride of soda, chlorate of potash, phosphate of potash, lime, and magnesia.

In small quantities (100.0 grammes) whey has no perceptible effect; in larger quantities (500 to 1000 grammes) it renders the stools easier, earlier, and more frequent, increases the quantity of urine and also of the perspiration in proportion to the state of the temperature. In regard to its effect upon assimilation exact information is wanting. As far as concerns the physiological and therapeutic action of whey, the salts contained in milk and the sugar of milk require attention. The sugar, by its decomposition, checks further disintegration of the albumen, fat, and glycogen in the body, and in this manner sustains the body in its existing condition, particularly when the organism is diseased and does not any longer retain power of assimilating adequate nourishment; in such case the operation of sugar is similar to that of alcohol. Although, when the body is in a healthy state, there is no necessity for introducing into it an excess of salts, this may become necessary in diseased states (fevers, suppurations, exudations, persistent catarrhal secretions of mucus, profuse sweats), which subject the body to a great loss of its salts (May).

Among the pathological conditions in which the systematic use of whey is employed, are found the derangements of the respiratory apparatus that take a chronic course, especially phthisis. The whey-cure is chiefly used in the beginning of the disease, if patients cough without much expecto-

ration, and while the local symptoms are still only slightly developed. It is necessary that the appetite and digestion should remain unimpaired and that there should be no tendency to diarrhœa. A low grade of fever does not seem to forbid whey in small quantities at this stage. On the other hand, when the local troubles are already advanced, when high fever supervenes, and when there is a decided tendency to sweat, the whey-cure must not be resorted to. In simple *chronic bronchial catarrh*, also, and in *chronic laryngeal catarrh*, benefit is sometimes derived from warm whey. The temperature in such cases is probably the main consideration.

There is no doubt but that the favorable result of the whey-treatment is mainly attributable to other causes. These causes are found first in the climatic conditions under which patients live while using the whey (the pure air); next, in the complete revolution in all the habits of daily life and all the well-known attendant circumstances. In many cases it also happens that the use of whey is accompanied with that water impregnated with a different mineral, sometimes from a spring impregnated with iron, sometimes from one impregnated with carbonic acid. In fact the observations which have been made do not furnish data upon which to form a definite opinion as to the efficacy of whey, when the patient remains under the original, unchanged circumstances, so as to determine whether the preparation in itself exerts any noticeable influence upon the progress of the disease under treatment, and if so, precisely what that influence is.

Occasionally whey is administered in heart-disease, more particularly when the atrioventricular valves are affected in case, compensation existing, there is a tendency to constipation. As a matter of course, under such circumstances whey must be given only slightly warmed. Experience, however, shows that in such cases when the constipation is great the remedy fails, and that on using still larger quantities of it, the digestion and appetite are apt to be injured, without producing the desired effect upon the excrementory discharges.

Where there is a predisposition to gout, in *plethora abdominalis*, etc., the whey-cure is decidedly less successful than other modes of treatment, and may therefore be dispensed with in such cases.

From external applications of whey, which have been tried in the most various forms (baths, clysters, injections), no favorable results have been obtained.

The quantity, form, and manner in which whey must be taken vary so much in individual cases that they must be determined upon when administered. We can only say that, as a rule, the use of enormous quantities has been abandoned and that now more than 1 to 1½ litre is seldom given.

Meat Peptone.—Under this head we treat particularly of the peptone manufactured by D. H. Sanders in Amsterdam, It is made from good beef, free from fat, by the use of pepsine (the active principle of gastric juice obtained from the stomachs of calves and pigs) and by the action afterward of pancreatine (obtained from beef pancreas). The peptone is in aqueous solution and concentrated so that one part is equivalent to three of good beef, free from bones, tendons and fat; thus concentrated, it does not decompose after having been exposed for years to the air.

Genuine peptone of this kind is dissolved quickly and completely in either hot or cold water; it is not under any circumstances precipitated from solution by acids, rapidly permeates parchment-paper and animal membranes, and does not appear in the urine after injection into the blood.

Peptone is easily dissolved in alcohol which is not too strong; it is precipitated by pure alcohol, although not wholly. When dried it readily absorbs aqueous vapors from the air. In aqueous solution it is not precipitated either by heat at the boiling point, or by mineral or acetic acid, even when carefully acidulated with diluted acetic acid; nor is it precipitated by alkalies. On the other hand, in neutral solution peptone is precipitated by tannic acid, chloride of mercury, and basic acetate of lead. Sanders-Ezn himself states the indications for meat peptone as follows, He says that it is found to be a suitable means of nutrition: (1) In all diseases and disorders of the organs of digestion; (2) In all cases where rapid and powerful nutrition is required and the digestive organs are not able to respond to the call (states of fever, convalescence, etc.); (3) In all cases in which nutrition by way of injection is resorted to. Information derived from various other quarters bears witness to the value of meat peptone; many patients, however, take it with reluctance under the circumstances mentioned. About 200 grammes of meat peptone daily are required for the sustenance of an adult.

Albuminous Solution of Vegetable Peptone (for diseases of the stomach and bowels, and for convalescents).—The best formula for its preparation, according to Penzoldt, is as follows: 250 grammes of finely ground peas, 1 litre of water, 1 gramme of salicylic acid (which like muriatic acid aids digestion and at the same time is strongly preventive of fermentation), and 0.5 grammes of good pepsine are thoroughly mixed and frequently stirred together, allowed to stand 24 hours in a warm place (not over 30° R.), then strained and somewhat evaporated with moderate heat. The soup thus produced may be flavored to suit the taste, with salt, spiecs or meat extract as may be desired.

A cheap albuminous solution containing peptone for nutritive clysters may be obtained from ground peas by pancreatic fermentation, by allowing 250 parts ground peas, 500 water, 1 salicylic acid, and 10 drops pancreas glycerine to digest 24 hours and then decanted.

Pepsine.—The gastric ferment, pepsine, which is obtained from gastric juice or the mucous membrane of the stomach in various ways, has precisely the property of natural digestion of reducing albuminous substances to an acid solution and of transforming them into peptone. The rapidity of the digestion induced by pepsine, within certain limits, increases according to the quantity of pepsine used; one and the same dose of pepsine, however, always exciting a new solvent action upon the albuminous matter subject to digestion, provided provision is made to supply hydrochloric acid in place of that consumed. Pepsine, like other digestive ferments (ptyaline, pancreatine, trypsine), is absorbed into the blood out of the digestive tract and transmitted to various organs (the muscles, liver, blood—Brücke, Cohnheim). Albertoni found that after injecting a sufficient quantity of good pepsine into the circulating blood of a living dog, the blood coagulated slowly and imperfectly and contained a much smaller quantity of fibrin than before the injection. Theoretically the therapeutic indications may be very easily formulated; as such, indeed, may be assumed all dyspeptic conditions which have for their cause a deficiency of pepsine generated in the stomach, or its abnormal quality. But in practice the matter stands differently: there is no case in which it can be determined with certainty in advance from the symptoms that *administration* of pepsine is indicated. The process of drawing gastric *juice from the* stomach by a stomach-pump and testing by experiment *its digestive efficiency* (Leube) is hardly available in practice, to say

nothing of the uncertainty of the results hitherto obtained from it. Reliance is therefore to be placed upon pure experiment. Pepsine is said to be efficacious in cases of dyspepsia resulting in anæmia and tuberculosis, with scrofulous children and old people, and in chronic catarrhs of the stomach. In all further cases as a remedy it is simply useless. Various kinds are known in commerce, in which the quantity to be given daily varies from 0.05 to 5.0. Ewald's investigations show that the efficacy of the varieties manufactured in producing peptone is different; we do not, therefore, deem it expedient, on account of the continual change that is possible, to refer in a hand-book like this, to the sources of supply of the article which have become reputed to be the best.

Pepsine Wine.—The article known in the pharmacopœia as pepsine wine (*vinum seu essentia pepsini*), according to Liebreich, is produced in the following manner: Fresh pigs' stomachs or rennet of beef stomachs are washed in fresh water and the secretion of the mucous membrane collected by scraping the membrane with a bone knife. Of the mucus collected 100 parts are then carefully mixed with 50 parts of glycerine previously diluted with 50 parts of distilled water. The mixture is placed in a large bottle, and 1000 parts of white wine, best quality, and 5 parts pure hydrochloric acid are added, and vigorously shaken; it is then allowed to macerate at a heat not exceeding 20° for 3 days, frequently shaken, finally filtered. The liquid is clear, yellowish, sourish, tasting of wine.

The indications for its use therapeutically are the same as for pepsine. But as glycerine merely serves to preserve the pepsine, which the spirits of wine do not, the action of pepsine wines, particularly those which have been kept long, is not at all reliable, and when effective it is possibly to be attributed to the alcohol and not to the pepsine. At any rate, in experiments made with the pepsine essences, they have been found to have hardly half the efficacy of pure pepsine (Ewald). Pro dosi 1.0 to 5.0, pro die 15.0.

Pancreatine.—Pancreatine is the ferment of the pancreatic glands, which peptonizes albuminous substances in alkaline solution, transforms starch into dextrine and sugar, and separates fats which have been emulsified in pancreatic juice into glycerine and free fatty acid. Satisfactory practical experiments for testing the value of this preparation have not been made; and as the various kinds of the article known to trade have been employed we refrain from pronouncing any opinion upon it.

GLUTINOUS SUBSTANCES.

Glutinous tissues (cartilage, tendons, ligaments, serous membranes, the derma) are only found in animal organisms, are insoluble either in cold or warm water, and by long boiling in water are transformed into glue. Bone-glue (glutine) is distinct from cartilage-glue (chondrin). Both are the product of albuminous matter, and are distinguished from it by containing a somewhat larger quantity of N and a somewhat smaller quantity of C.

GENERAL PHYSIOLOGICAL CONSIDERATIONS.

Of the tissues yielding glue, cartilage and tendons undergo very little digestion in the stomach and intestines; on the other hand, serous membranes are dissolved in great part therein.

Glue in itself is tasteless, is transformed in the stomach into a liquid substance (glue peptone), and, according to Voit, is rapidly taken up by the blood and completely disintegrated in the body. An increase of the excretion of urea follows the ingestion of glue.

Small doses do not have any apparent effect; large ones disturb digestion.

The nutritive value of glue is not as great as was formerly supposed; according to Voit, its significance in this regard consists (1) Instead of disintegrating the albuminous matter which is in the circulation, but by preserving it it checks the consumption of organic albumen; (2) It prevents the destruction of a small part of the fat in the body. It is, however, incapable of forming organic albumen or as material for the formation of cells, and thus in tissue metamorphosis it acts similarly to fats or the carbohydrates.

THERAPEUTIC APPLICATION.

The administration of glue internally for therapeutic purposes does not offer any benefit or advantage over other remedies. In inflammations of the digestive organs, in which it has been used as a vehicle for other drugs, it presents no advantages over mucous or fatty substances. A possible benefit in diseases of the respiratory apparatus has by no means been established.

As a means of nutrition glue is not used alone. Experience, however, has shown, and this finds some support in Voit's investigations, that glue in conjunction with other substances is sometimes of use. For example, atrophic, scrofulous, and rachitic children thrive better on milk to which veal broth (which contains the most glue) has been added, than on milk alone. Senator has lately pointed out the advantage of glue as food for fever-patients.

Externally glue has manifold applications as an adhesive *coating* substance; pharmaceutically it is used in the preparation of gelatine capsules, which are useful in taking

drugs that have a bad taste or cause irritation in the mouth.

White glue, gelatina alba, is prepared from fresh cartilage, calves' feet, in the form of small, thin, colorless cakes.

All that has been said above, generally, of the action and use of glue has direct application to the use of gelatine. As a meaus of nutrition it is used in the form of portable soup-cakes; pharmaceutically it is used in making gelatine capsules (*capsulæ gelatinosæ*) and for coating pills.

Fish-glue, colla piscium (isinglass, ichthyocolla) prepared from the air bladders of several kinds of sturgeon (acipenser huso).

Internally this substance is of no use whatever; it is at most serviceable in the kitchen in the preparation of jellies. But when used medicinally, the dose is 5.0; 200.0 to 400.0. Externally, ichthyocolla is used in the preparation of court-plaster.

Emplastrum adhæsivum anglicum seu taffetas adhæsivum.—One part of isinglass is boiled in a sufficient quantity of water until colature in 12 parts of water is produced; of this, half is laid upon silk taffety or gold-beater's skin, and the other half is mixed with 4 parts of alcohol and $\frac{1}{10}$ part of glycerine, and painted, upon the coated taffety. The thinner the layers in which it is painted and the greater their number, the more adhesive and tenacious the plaster proves. The preparation is finished by painting the back with tincture of benzoin.

Glycerine and Fats.

Glycerine.

Glycerine, $C_3H_5(OH)_3 = CH_2.OH - CH.OH - CH_2.OH$, is an alcohol which differs from the monatomic, and diatomic alcohols (æthyl-alcohol, æthylic alcohol, etc.) in that it contains three atoms of hydrogen replacable by radicals.

It is a colorless and odorless heavy fluid, of a sweet taste. It is easily soluble in water and is not readily soluble in alcohol, ether, chloroform, or the heavy oils.

PHYSIOLOGICAL ACTION.

Glycerine is consumed as such in many aliments, as for instance in wine, beer, roast meats. Large quantities of glycerine are separated from the fats that are being digested and from the fæcal masses, and is reabsorbed.

It is strongly hygroscopic, and thereupon depend some of those few of its effects which are thus far known. The *skin* takes it up readily and is rendered soft and pliable by it. Very concentrated glycerine produces a slight inflammation and faint burning in ulcers and on the mucous membranes. No peculiar action of glycerine, at least when diluted, upon the stomach and intestines is known; even after taking 15.0 grammes nothing abnormal has been observed.

From the intestines it is probably easily transmitted into the blood-vessels and chyle-ducts; for it is always produced by the digestion of fat in the small intestines, inasmuch as the pancreatic juice transforms all fats into glycerine and fatty acid.

The transformation of glycerine into glycogen and other substances that form and resemble sugar in the blood and tissues has not been at all demonstrated. Deen's assertion that it is partially transformed into sugar by nitric acid, and Berthelot's that it is transformed into sugar by fermentation, have been shown to be erroneous. Huppert and Perls have shown that the reduced substance supposed by Deen to be sugar is not really sugar, but a volatile matter; Berthelot was probably deceived by the sugar which is developed from the glycogen when the tested substance is exposed too long.

Schultzen's opposite suggestion that glycerine induces combustion of sugar in the animal organism, and therefore is the most effectual remedy for diabetes, has been controverted by most investigators.

On the other hand, Luchsinger and Ustimowitsch have made us acquainted with the following effects of glycerine: After the introduction of glycerine into the stomach, and somewhat more slowly upon its direct introduction into the blood, by way of injection, that is, within an interval of four to fifteen minutes, an acceleration and *increase of the excretion of urine takes place*, resulting, partly, from the property of glycerine to appropriate water, partly from a dilution of the blood, and the urine becomes as clear as water.

After the secretion of urine has reached its maximum rapidity, the incorporation into the stomach or the introduction under the skin is followed by gradual coloration of the urine; the urine, which previously was pellucid, becomes straw-colored, then gradually passes to reddish, and finally becomes deep red like wine or blood. *This coloration results from the appearance of hæmoglobin in the urine;* and the transmission of hæmoglobin into the urine is produced by the gradual decomposition of the red blood-corpuscles; many of the blood-corpuscles are reduced in size, the number of those that remain intact is diminished, the serum becomes dark red (in frogs, rabbits, dogs, and men). It is remarkable that the same quantity of glycerine which, *diluted with water*, surely generates hæmoglobinuria by its *introduction into* the subcutaneous connective tissue and

into the intestines, does not have the same effect when directly injected into the blood of dogs or rabbits; the same glycerine directly mixed with animal blood does not produce any noticeable effect upon the form and color of the blood-corpuscles; whereas when diffused through the blood it withdraws from the blood's plastic lymph a series of substances (particularly chlorides and sulphates) which are indispensable for the maintenance of the integrity of the blood-corpuscles, and thus directly frees the hæmoglobin and the coloring matter of the blood; and this is the most probable explanation of the remarkable facts above mentioned (Eckhardt—Schwahn).

A further property of glycerinous urine is that it *reduces* the oxide of copper on the application of the gentlest heat; both the colorless and the reddish urine is susceptible of fermentation, and when in the presence of a ferment it disengages carbonic acid. The reduced matter is not, however, sugar, but probably some substance resulting from the disintegration of glycerine, the nature of which is not yet understood (Ustimowitsch).

The operation of glycerine in this respect seems to be identical both in healthy and diabetic animals.

With regard to its operation in other respects it is only known that its property of appropriating water causes it to act upon frogs in the same manner as common salt or sugar does, without, however, inducing cataract (Husemann); and concentrated glycerine, likewise, produces tetanus upon nerves, but upon muscles freed from nerves it does not produce even twitching.

As regards the significance of glycerine in *nutrition* and tissue metamorphosis, it must in the first place be mentioned that in the small intestine nutritive fats are separated into glycerine and fatty acids, which must be united again in the body; that is to say, in the adipose cells, as we will explain more in detail under the head of Fats. The fact to which Radziejewski and Kühne have called attention, that quantities of fat are deposited in the body, while sebacic acid is only introduced in lean meat, shows that fresh glycerine may be generated from albumen in the body.

According to J. Munk, glycerine, at most, can only serve by its disintegration in the organism as material for the generation of heat, but is incapable of preventing destruction of even minute quantities of albumen, and, in his opinion, it therefore has not the slightest nutritive value.

According to L. Lewin, also, glycerine does not produce any diminution of the decomposition of albumen, but, at least when large quantities are taken (on an average of eleven experiments about 1 gramme per diem), a small increase of it, as he supposes in consequence of glycerine's quality of appropriating water and the increased secretion of urine produced thereby, as, according to Voit, the increased circulation of water alone increases the decomposition of albumen. If, therefore, even Lewin is compelled to deny that glycerine has the property of economizing albumen, he does not deem it impossible that glycerine may, perhaps, impede the waste of fat in the body and therefore serve as a food, similarly to the fats and the carbohydrates.

With regard to what becomes of the glycerine set free in the body upon the disappearance or disintegration of fat, the experiments of Gorup—Besanez afford the materials upon which to form an opinion. In them, glycerine in alkaline solution is rapidly transformed by free oxygen into propionic acid, formic acid, and probably into acrylic acid.

THERAPEUTIC APPLICATION.

It has been principally employed for external application; its use for various internal diseases has also, of course, been tried. Thus, it has been recommended in scrofula and tuberculosis as a substitute for cod-liver oil. No satisfactory observations have as yet been placed on record which justify this recommendation. It has been used as a protective coating in ulcerative processes in the larynx, and furthermore in intestinal catarrh and ulceration of the intestinal mucous membranes; but in these cases, also, it has not been proven that glycerine has any peculiar efficacy above other means. Schultzen recommends glycerine in *diabetes mellitus* as a substitute for sugar. Observations instituted to test the recommendation show that in fact, when used, the excretion of sugar sometimes diminishes; such cases, however, are rare, and the rest of the symptoms are not affected at all. Inasmuch as, at present, the almost entire insignificance of glycerine in the therapeutics of diabetes has been established, it seems superfluous to go in detail into the numerous theoretical controversies to which Schultzen's recommendation gave rise.

The external applications of the preparation are manifold; *that is, particularly* in almost all the cases in which the

usual fatty oils are used. Over the latter, however, it does not possess any such extraordinary advantages as have been of late imputed to it, with the exception that it does not turn rancid.

One of the properties of glycerine is important, viz., that of holding in solution a long list of active remedial agents (alkaloids, vegetable extracts, and metallic salts that are soluble in water); this property renders its use for pharmaceutical purposes very extensive.

Dosage and Preparations.—1. *Glycerinum*, from 1.0 to 5.0 pure, or mixed with water. 2. *Unguentum glycerini*, 2 parts starch, 10 parts glycerine, 1 part water, used alone or as base for other substances.

Fats.

All kinds of fat that occur in nature at ordinary temperatures are partly solid (tallow), or intermediate (butter, lard), or partly liquid (oil). The first two, however, become liquid at high degrees of temperature; they are all lighter than water and insoluble in it; while few of them are soluble in alcohol, all of them are so in ether. Not one of the fats or fatty oils is volatile.

All fats are neutral compounds of glycerine, $C_3H_5(OH)_3$, with the so-called sebacic acids ($C_nH_{2n-1}O.OH$) and oleic acids ($C_nH_{2n-3}O.OH$) = $C_3H_5(O.C_nH_{2n-1}O)_3$ and $C_3H_5(O.C_nH_{2n-3}O)_3$, particularly of the palmitinic, stearic, and oleic acids; however, no natural fat is composed of a single glycerine of any one of the fatty acids alone, but several of these are always combined.

By boiling with strong basic alkalies, fats and fatty oils are resolved into soluble sebacic-acid alkaline salts; that is, soap (compare page 81) and free glycerine. If fats are boiled in water with protoxide of lead, insoluble sebacic-acid salts of lead (diachylum plaster, p. 136) are formed and the glycerine remains in solution in the water.

In the air also, in a manner not precisely understood, fats become decomposed (rancid) and resolved into glycerine and fatty acids; and the latter undergo still further decomposition. In the intestines fats are likewise separated by the pancreatic ferment into their two constituent elements.

All fats, as far as they are pure, are colorless, odorless, and tasteless; but in the form in which they are found, the most various substances are mixed with them, and of course, derive from these substances different colors, odors, and tastes.

PHYSIOLOGICAL VALUE AND ACTION.

Fats are found in great quantities in the different organs, and are in part derived from the fats, the carbohydrates, and the albuminous matter taken in food. In opposition to some doubters, F. Hoffman has established beyond all dispute that fats taken in food really go over into the organism. That fat is formed in the body from the carbo-

hydrates and albumen received has not indeed been proved as yet beyond all question, but it is very probable. That it is possible to produce fattening more rapidly by food containing starch-meal and sugar tends to show that fat is formed from the carbohydrates; as does also the proof furnished by various series of experiments that the large quantities of fat found in the body are not to be attributed either to the fats taken in food nor to the nitrogenous substances; as also the fact that bees fed exclusively on sugar continue to produce wax. And from the accumulation of the carbon from meat in the body at the same time that all the meat-nitre is eliminated (Voit), and from the fact that fat is generated more copiously upon exclusively albuminous nutrition, the conclusion is drawn with greater probability that fats are generated from albuminous matter; it is less probable that it is produced by the fatty degenerations of the muscular cells.

How Disposed of in the Organism.—The fats do not seem to undergo much, if any, change in the mouth, œsophagus, or stomach; on the other hand, in the intestines, by the bile and pancreatic juice, they are partly changed into small drops of fat and partly resolved into their constituent elements, glycerine and fatty acids. The fatty acids when set free unite with the alkalies of the intestinal contents and form soap, and emulsify the fat which has not yet been transformed. The small drops of fat, in some way which has not yet been positively ascertained, enter the chyle-ducts, and thence pass into the blood; in like manner the glycerine thrown off and the soap formed are taken up by blood, so that when the supply of fat is not inordinate no fat whatever or any of its constituents are found in the lower parts of the intestinal canal.

The fats taken up into the circulation are then for the most part deposited in the fat-cells; and yet fat is found in several other cells (for example, in the muscle-cells). The absorbed constituents, glycerine and fatty acid, may either in part combine in the cells mentioned and form glycerides, but are also again oxydized, as well as the fat itself, and then resolved into the various fatty acids first, and afterwards burned into carbonic acid and water, and eliminated as such. Fat is, however, also eliminated unchanged by *means* of milk and sebaceous matter. Only when fat *has been taken* in inordinate quantities it is found in the *urine.*

The Action of Fat upon the Skin and Digestive Tract.—Rubbed upon the skin, fat softens and lubricates it and impedes evaporation. All oily matters pass through intact skin, even when covered with hair, and find their way through the lymphatics and blood, and are finally excreted by the kidneys. If the skins of rabbits are painted or smeared with rape-seed oil, olive-oil, or cod-liver oil, they are found to be emulsified (and the emulsion has the characteristics of the identical kind of oil used) in the serum and in each organ. The viscera of a rabbit anointed with cod-liver oil have a strong smell of the oil in question; the liver, lungs, and kidneys are besprinkled with numerous fine drops of fat; the uriniferous duct is dilated by large drops of the medicament with which the animal was smeared, and the subcutaneous connective tissue is most copiously impregnated with it. The indifferent fats and oils, the non-drying glyceride of oleic acid (olive-oil, rape-seed oil, cod-liver oil) traverse the renal epithelia unchanged. On the other hand, the drying oils, to which linseed-oil belongs, undergo oxidation and rapid hardening in the air, or in any other contact with oxygen (consequently also in the blood), andmust produce the same injurious effect upon the tissue of the kidneys as petroleum or the tincture of cantharides does (Lassar).

According to Fourcault, a permanent and complete coating of fat over the whole skin; in the case of many kinds of fat produces effects similar to those of a coat of varnish; such as depression of temperature, increased excretion of urine, albuminuria, gradual retardation of respiration and of the pulse, and death. The causes of this remarkable result are not known to have been discovered with certainty; according to Laschkenitsch, they probably are due to the enormous cooling occasioned by dilatation of the superficial vessels. Lassar attributes the albuminuria to the increase of the transmittent power of the epithelia upon passage of irritating fatty substances (resins), and bases his conclusion upon the trial of injections of innocuous, non-diffusive aniline blue and indigo carmine; the causes do not consist in obstructions in the vascular circulation.

In this connection, especially, Lassar draws attention to the practice popular with the older physicians of prescribing embrocations of fat or cod-liver oil for phthisical patients who are unable to take fat *per os*, and shows that the *injudicious* external application of substances which,

like petroleum and cantharides, are readily absorbed, is dangerous, and may irreparably damage the tender renal epithelia.

Small quantities of fat do not cause any symptoms of disease. Large quantities on the other hand impair the appetite, produce nausea, even vomiting; these effects, however, may be prevented or at least mitigated by alcohol. As a large part of fat, when taken in excess, does not undergo any transformation, nor is absorbed, the excrements contain a large quantity of fat, and hence are lubricated and are evacuated more readily.

If too large a quantity of fat finds its way into the circulation—for example, by absorption from extensive purulent foci—fatty embolism may occur in the pulmonary vessels and result in death.

Effect upon Nutrition and Tissue Metamorphosis. — Life cannot be sustained upon nutrition consisting of fat exclusively; it causes animals to perish with anorexia and inanition.

Fat taken in connection with albuminous food has the effect of causing corpulence.

In dogs deprived of food, the daily excretion of urea continues uniform until all the fat contained in their bodies has been consumed; as soon as a deficiency of fat arises, a thing very likely to occur, the excretion of nitrogen is at once greatly increased.

Vice versâ, if the supply of albuminous food is kept the same, and more fat is supplied, the excretion of urea diminishes.

On account of the large proportions in which carbon and hydrogen enter into the composition of fat, before it is finally resolved into carbonic acid and water, it requires enormous quantities of oxygen. If, therefore, much fat is present in the body or added to it, the oxygen brought into the body by respiration has an excellent material for combustion, and, as it resolves it into carbonic acid and water by the process of combustion it produces much heat. Fat is thus an excellent heat-generating material in the animal organism, and hence the predilection manifested for it in the frigid zones and during winter. In addition to this, a thick lining of fat under the skin lessens the radiation of heat, and thus retains heat in the body. But when the oxygen finds sufficient fat, it consumes less albumen; whence the diminution in the waste of nitrogen with the

increase in the supply of fat, above mentioned, and the increase in the waste of nitrogen when there is a deficiency of fat. Fat is, therefore, an excellent means of economy; inasmuch as it tends to retard the consumption of albumen in the body, it lessens the supply of albumen the body requires for repair and also for nutrition.

The fatty acids have the same significance as a means of economy as fat itself; when the weight of nitrogen in a dog attains the normal ratio to his whole weight on a diet of meat and fat, and if he is fed for twenty-one days with the fatty acids contained in the fat, instead of with the fat itself, the above normal ratio will be maintained. These acids are absorbed principally in the form of an emulsion and while on the way from the intestinal cavity to the thoracic duct a transformation into fat (that is, a synthesis—the source from which the organism derives the glycerine requisite) is for the present not manifest (J. Munk).

Animal and vegetable fats present no material physiological differences.

THERAPEUTIC APPLICATION.

Aside from the physiological significance of fat, direct remedial application is made of it in certain pathological states. This occurs particularly in *chronic diseases of the respiratory apparatus*, which advance with emaciation and wasting of the adipose deposit and muscle, as in phthisis. In this connection, use is made above all of cod-liver oil, then, to some extent of adipose milk; a diet, varied in other respects, but as plentifully supplied as possible with fat (butter, rich gravies, etc., and for ordinary use, according to the region of country, lard, dog's fat, buffalo grease, and bear's fat). The details of these "fat-cures" and their methods of application have been treated of under the head of milk and cod-liver oil. The grounds have been stated above upon which the great importance of fat for nutrition stands, and the reason why it tends to counteract the increase of the disintegration of nitrogenous material and the wasting of the muscle. In our judgment, however, these "fat-cures" have no specific value in direct application to phthisical affections of the respiratory apparatus, but benefit may be expected from them from the outset in other states in which the waste of

muscles and adipose matter results from an increased disintegration of matter or from a direct diminution in the material for nutrition. Thus, for example, in suppurative processes in the bones, we find in practice, that the administration of cod-liver oils proves efficacious. The reason why such fat-cures can not be resorted to in prolonged feverish conditions, and of exhausting diarrhœa is obvious; as the digestive apparatus commonly participates and the introduction of fat becomes impossible.

Use is made of fat internally in certain pathological conditions of the digestives apparatus—chiefly in *acute corrosion of the mucous membrance* of this apparatus—as a protective means. These cases are most frequently the result of poisoning by acids or caustic alkalies. Fats then, as a matter of course, are mere makeshifts; they do not dispense with the administration of the legitimate antidotes suitable for the particular case. Furthermore, it is hardly necessary to remark, that in such cases large quantities of fat must be given.

In all other inflammatory, dyspeptic, and other diseases of the stomach, fats must be absolutely avoided, because they tend to still further impair the appetite and digestion. There is only one other state in which (according to Traube) they may be successfully administered in small quantities. This condition appears as the accompaniment of other diseases, particularly of consumption, and is characterized in its lower degrees by a diminution, seldom by a total cessation of the appetite. During the period of digestion disagreeable sensations occur in the region of the stomach—and this is to be regarded peculiarly as a symptom,—the tongue is not coated, and, on the contrary, has a smooth, red, and glossy appearance; in the more severe forms it looks as if it had been lacquered. In this state, especially when there is no tendency to diarrhœa, fat is sometimes given with success, preferably in the form of an emulsion.

Ordinarily fats are seldom administered by themselves as direct purgatives, because their action is not strong enough; they may, however, be used particularly in aid of other aperients when the object is to evacuate hardened fæcal masses. Their action in promoting the discharge of *fæces is* purely mechanical, by lubricating them and the *inner surface* of the intestinal canal. Of course, large *quantities of* fat must be given for this purpose.

Fatty oils are often given for *violent irritating coughs;* in such cases, they are usually administered in the form of emulsions with the addition of some narcotic. Patients often profess to perceive some diminution of the tendency to cough; if this favorable result is obtained, it may be because the fats come in direct contact with the pharynx and the upper surface of the epiglottis. The result, however, seems to us to be rather due to the morphine, atropine, etc., administered at the same time. It is not at all probable that oils are of use in gonorrhœa and inflammation of the bladder as has been supposed, as other additional treatment is always resorted to in such cases; therefore the success cannot possibly be known to be due to the fat, and *a priori* it is not conceivable, as it is not possible, that any oil should get into the urine, when the quantity administered be considered. In regard to the circumstances which forbid the use of fats, in order to avoid repetition we refer to the subject of cod-liver oil, in connection with which they chiefly need consideration.

Manifold application is made of fats *externally*, aside from their use pharmaceutically for ointments, etc.; in this connection we refer directly to the results of Lassar's experiments, given in the section on physiology, by which it appears that fats are absorbed directly through the skin. Their principal use is as a protective covering in many illnesses connected with injury to the epidermis; thus, occasionally, in recent wounds; in suppurating wounds which look "irritated" and inflamed, and which do not secrete freely, and in burns. They are used, further, in a special series of so called skin diseases, partly in order to furnish a protecting coat, partly in order to render the skin more supple. In several kinds of inflammation of the skin they are also employed, but it is not precisely clear upon what the favorable result depends. For the purpose of checking excessive perspiration, embrocations of fat are of very subordinate benefit; in such cases they perhaps only serve to allay the stiffness of the skin in the intervals between the sweats. Very often fatty embrocations (warm) are used in more deeply seated inflammations (even in pleurisy, peritonitis), and it must be said not without benefit. It may be that a fraction of this benefit is due to the mechanical action of rubbing in the embrocation, but, nevertheless, the principal part is to be ascribed to the protection afforded by the layer of fat and its action in retaining heat,

in which it is aided by the superimposed wadding. Later on we will discuss embrocations in general, especially as used in scarlet fever.

Internally, oils are given pure or in emulsions, according to the effect desired; externally, they may either be used pure or in ointments or liniments.

Animal Fats Containing Nutritive and Remedial Substances.

In addition to the albuminous nutritive substances of the animal kingdom of which we have treated (milk and animal fats), the following fatty require to be mentioned:

Butter (*butyrum lactis*). Composed of a large number of glycerides of the most various fatty acids, solid, liquid, and volatile, by the liberation of which it readily becomes rancid.

Lard (*lardum*), especially hog's lard. Lard is seldom employed internally for direct therapeutic purposes; in many districts it is in repute as a popular remedy in pulmonary consumption. Recently it acquired a temporary reputation, having been used in scarlet fever, for systematic embrocations. The advantages for which this treatment was recommended by Schneemann have not been confirmed by observers in other epidemics. It is well known that epidemics vary in character, and that while in one a complication (diphtheritis, nephritis) is extremely common, in others it is entirely absent. It is possible that Schneemann happened to have had favorable epidemics. Besides, it is possible that a considerable part of the favorable results he obtained is to be ascribed to the other treatment he adopted, such as free ventilation, and keeping the temperature of the sick chamber at a low point, even down to 10°. The sole advantage in lard embrocations in scarlet fever, which at the present time is beyond question, is that they render the skin more pliant. What is true of scarlet fever also applies to measles. Mention may be made of the popular practice of laying a rind of bacon with the fat side next the throat in laryngitis; it operates partly as a warm poultice, and partly as a gentle irritant (the skin becomes red and small pustules form).

Pork fat or lard, Adeps suillus (*Axungia porci*). Fresh and pure it is of a clear white color, free from smell and tasteless.

The most frequent use made of pork grease is as a base for ointments; no doubt it is the cheapest material for this purpose; only the ointments prepared with *axungia porci* have the disadvantage of readily rancidifying.

Unguentum rosatum, rose salve, 10 parts *adeps suillus*, 2 parts *cera alba*, 1 part *aqua rosarum*.

As pork fat is used in Germany as a popular remedy in pulmonary consumption, so is goose fat and dog's fat. In America buffalo grease and bear's grease are used.

Tallow (*sebum*), the fat of sheep, beef, deer; it has greater solidity on account of the predominance of stearine in it. In the pharmacopœia *sebum bovinum*, only, is used.

Cod-liver oil (*oleum jecoris aselli*). Cod-liver oil is a liquid fat obtained principally from the liver of the *gadus morrhua* (cod), but is also obtained from other fishes of the cod species. There are several varieties:

1. A colorless or faint yellow variety, which has a slight fishy smell, tastes mild, hardly at all scraping, and is of a neutral or acid reaction; it is yielded by fresh fish livers warmed (*oleum jecoris album seu flavum*). 2. A yellow variety, which is, however, quite transparent; has a strong, fishy smell, a biting taste and acid reaction, and runs spontaneously from livers packed in casks (*oleum jecoris subfuscum*); and 3. a brown kind (*oleum jecoris fuscum*), which in the end is boiled off; the darker the color the more disagreeable are the smell and taste.

In German pharmacy no difference is made between these three varieties. Cod-liver oil is frequently adulterated with vegetable oils; care must therefore be taken as to the sources from which it is obtained.

According to Buchheim, cod-liver oil differs from most of the other heavy oils in containing, in addition to the glycerides (especially oleine), free fatty acids (oleinic acid, palmitinic acid, stearinic acid); the quantity of these free acids is less in the lighter colored varieties than in the darker, and averages 5 per cent.

The assertion formerly made by Naumann that elements of bile are found in cod-liver oil are disputed by Buchheim upon the ground of direct experiments, and by the consideration that, with the exception of cholesterine, all the constituents of bile in fat oils are insoluble.

Cod-liver oil also contains a small quantity of iodine (0.02 per cent), bromine and trimethylamine.

PHYSIOLOGICAL ACTION.

The ideas that the traces of iodine and bromine in cod-liver oil cannot possibly exercise any influence, or that cod-liver oil owes its value to them, do not require discussion now. Its operation cannot, with any more reason, be imputed to the bile constituents, as, according to Buchheim, it has none; hence, Klenke's suggestion that cod-liver oil ought to be regarded as a substitute for bile, requires modification.

O. Naumann was the first to make known a property of cod-liver oil which is of material importance with reference to its use; it penetrates animal membranes with greater ease than do the other heavy oils, and for this reason cod-liver oil is absorbed more readily than the others. Naumann was still in the belief that cod-liver oil had bile-constituents, and, therefore, he ascribed this property to the presence of these constituents. After Radziejewski had suggested that its therapeutic benefit was perhaps attributable to the large quantity of oleic acid it contains, Buchheim proved that what Naumann had taken for bile, was in fact free fatty acids, and he proved that it is these that give the cod-liver oil its power of ready absorption. Radziejewski and Kühne showed by experiments that simple fatty acids or soaps, in combination with lean food, form immense quantities of fat in the body, notwithstanding that no glycerine is added, so that the glycerine must be separated from the albumen in the body. It is to be remembered further that cod-liver oil is often difficult of digestion on account of the numerous glycerides it contains. Buchheim, therefore, is right in asking whether it would not be advisable to abandon introducing the glycerides and to use the free fatty acids in their place, as the latter are certainly absorbed with more ease than the glycerides. By way of experiment he recommends the use of oleic acid pure, or mixed with glycerides in certain ratios which are still to be ascertained. More certain results would probably be obtained in this

manner than from the cod-liver oil, which is uncertain by reason of the varying quantity of fatty acids it contains.

As æther administered internally increases the secretion of the pancreatic juice (Cl. Bernard) the digestion of cod-liver oil may be promoted, according to Foster, by allowing the patient to take it with the oil or a short time afterward.

At any rate, cod-liver oil is of value only as a dietetic remedy and its use is to be regarded as a cod-liver oil or fat cure (Buchheim).

THERAPEUTIC USE.

Cod-liver oil was employed long since in the countries where it is obtained as a remedy, and during the last few decades its use has been extended far and wide. The conditions in which the greatest benefit is to be expected from it are as follows:

In the first rank stand chronic, wasting diseases, in which the progress consists in the dissolution of the parenchyma of the lungs; the various forms of pulmonary consumption. No further argument is required to show that cod-liver oil does not exert any direct healing influence upon the diseased process in the lungs, as now and then has been assumed; nor is any direct effect produced upon the symptoms relating to the respiratory apparatus. Moreover, there is a total absence of trustworthy statistical material, whether the rate of mortality in phthisis has diminished since the introduction of cod-liver oil into use; hardly a single physician can affirm from his own personal experience, that he has saved the life of more consumptive patients with the use of cod-liver oil than without it. It has gained its reputation in the treatment of consumption from being, under proper circumstances, an excellent means of nutrition for patients suffering from diseases of chronic consumption; *its value not only in phthisical diseases of the respiratory organs, but in other conditions, is mainly that of a "fat-cure"* (compare page 811); and as far as regards nutrition in the treatment of pulmonary consumption, cod-liver oil is of great value. By using it in connection with other nutritive substances the weight can be rapidly increased; and when in rare cases the morbid process is merely arrested in its progress, as, for example, sometimes in caseous (tuberculous) pneumonia, nevertheless it seems as though cod-liver oil had wrought a cure. But for the administration of cod-liver oil, it is necessary that certain special circumstances should exist and certain precautions be taken in its administration. These have been stated by Traube as follows: It must not be resorted to while fever is present and the local affection is progressing rapidly. It is only when the patient is free from fever, when the symptoms of acute inflammation have disappeared and the patient is pale and emaciated, that cod-liver oil comes into play, provided that two other indispensable prerequisites are also fulfilled, namely, the appetite must be very good and there must be no tendency to diarrhœa. The particular stage of the disease is of no consequence: cod liver oil is seen to exert its nutritive power sometimes as strongly where there is a considerable formation of cavities as where very slight physical changes can be detected, always provided the above mentioned conditions exist.

In various other states, accompanied by diminution of the bodily weight, *cod-liver* oil has been resorted to, but with little success. If a trial of it *is desired, care must* be taken to pay attention to the contraindications *above mentioned.*

In *scrophulosis*, cod-liver oil is found to be the best of all internal remedies in connection with iodide of potassium. The partial conflict in experience shows that it must be given, as a matter of course, in all cases; but the treatment must be adapted to the circumstances of each case. Upon the whole it appears, to use the old clinical expression, that cod-liver oil is of the most use in the so-called "erethismic" form of scrofula, and so would serve as a kind of complement to iodine. Above all, it is useful in scrofulous affections of the bones (caries, necrosis, *spina ventosa scrophulosa*); then in scrofulous affections of the skin; also in ulcerative affections of the mucous membrane, ozœna, etc. It is of much less use in scrofulous affections of the glands, particularly when they have not yet ulcerated.

Aside from the exact individualization of a particular case, even when it seems to be suited for treatment with cod-liver oil, attention must be paid to a succession of points which may sometimes amount to a complete contraindication of the remedy. At the same time we would here remark that a part of the circumstances may forbid the application of other fats under other conditions. In the first place it has been ascertained that children during the first months of their life, say up to the end of the seventh month, cannot bear cod-liver oil at all; at this tender age, it is best to avoid it altogether. Further, it ought to be employed with extreme caution or not all where there is a great abundance of fat or a tendency to corpulence, as sometimes is the case in what is called the torpid form of scrofula. Moreover, it is of little benefit, and it sometimes may prove even hurtful when the skin's activity is reduced and the skin is stiff and dry. Further, it acts badly where there is a "tendency to inflammation" and to hemorrhage and in "general plethora" (according to the expression of the older physicians). Cod-liver oil is positively contraindicated where there is any disturbance of the digestion and where there is a tendency to diarrhœa. And finally, experience has shown that, where the patient declares a repugnance, if nausea and vomiting continue after using it for eight days, forcing the use of the remedy upon the patient longer is mischievous.

To scrofula we would add rachitis, in which favorable results are often obtained with cod-liver oil; the necessary dietetic treatment being of course followed at the same time. It would seem that the most benefit is derived where the affection of the bones preponderates, and the symptoms regarding the alimentary canal are less developed. In what is called *acute rachitis* with marked participation of the alimentary canal in the disease, cod-liver oil must not be given, and as a rule, the contra-indications are the same as in regard to scrofula.

Dosage.—For most persons the most agreeable manner of taking cod-liver oil is to swallow it pure; none of the emulsions, linctus, etc., make it any easier to take. Coffee may be drunk afterward, or some oleo-saccharum (peppermint, lemon) may be taken, to cover the taste. It is advisable to begin with moderate doses, one half tablespoonful twice a day with adults, one half to two teaspoonfuls with children according to their age; the dose cannot be made to exceed four tablespoonfuls, except very rarely, without disturbing the digestion.

Of the various kinds of cod-liver oils found in the market at present, according to Almén and Husemann, that of H. Meyer, of Christiania, and known as "Natürlicher Medicinalthran, *Oleum jecoris aselli naturale*," ranks the highest.

ANIMAL SUBSTANCES CONTAINING WAX

Beeswax (*Cera alba et flava*). This is a fatty substance, but which differs from most of the other fats by containing, in place of glycerine, another alcohol, the melisylalcohol, and therefore is to be regarded as a compound of the latter, or as palmitic acid, melis sylestrum, $C_{30}H_{61}O$. $C_{16}H_{31}O$.

Wax is not absorbed by the stomach or alimentary canal, and is found in the excrement unchanged. For pharmaceutical purposes it is used in the preparation of cerates, ointments, plasters, charta, and linteum ceratum, bougies, etc.

Unguentum cereum, 5 parts *oleum olivar.*, and 2 parts *cera flava*.

Spermaceti, *Cetaceum* (*sperma ceti*), is the fat obtained from various species of whale—for example, the sperm whale, physeter macrocephalus,—and is a white, shiny, crystalline substance of a waxy consistency. Like wax, it contains no glycerine, but in place of it cetylalcohol (æthal) and is principally a palmitic-cetylester, $C_{16}H_{33}OC_{16}H_{31}O$. Was formerly used internally (in bronchitis, phthisis); is utterly useless. Employed externally in the preparation of plasters and ointments.

Dosage and Preparations.—1. *Cetaceum saccharatum*, 1 part with 3 parts sugar. 2. *Ceratum cetacei*, *emplastrum spermatis ceti*, consists of 2 parts each, cera alba, cetaceum, and 1 part oleum amygdalarum; used for application to wounded spots. 3. *Ceratum cetacei rubrum seu labiale rubrum*, red lip-salve, 90 parts ol. amygd., 60 parts cera alba, 10 parts cetaceum, 4 parts rad. alkannæ, 1 part, each, ol. bergamottæ and citri. 4. *Unguentum leniens*, cold-cream, 5 parts cetaceum, 4 parts cera alba, 32 parts ol. amygdalarum, 16 parts aqua rosæ, 1 drop ol. rosæ.

REMEDIES AND NUTRITIVE SUBSTANCES DERIVED FROM THE VEGETABLE KINGDOM.

Olive oil (*Oleum olivarum*) is obtained from the olive, olea europea. Two varieties are known: Provence-oil (oleum olivarum optimum seu provinciale), and olive oil, or sweet oil, (oleum olivarum commune); it consists in the largest part of the glyceride of oleic acid (oleïne).

Internally, *oleum olivarum* is administered either pure, or in the form of emulsio oleosa (2 parts oil to 1 part gummi arabicum).

Almond oil, Oleum amygdalarum, is obtained from sweet and bitter almonds (amygdalus communis) and has the most agreeable flavor of the vegetable oils.

All that was said of the action and use of olive oil is true of almond oil, only for practical purposes the higher price of the latter has to be taken into consideration.

Sweet almonds, semen amygdali dulce (amygdalæ dulces), contain a large quantity of the last mentioned oil and albuminous substances also; hence, they cannot be regarded as pure adipose nutrition.

An emulsio vera can be made of almonds alone, without addition of gum (15.0 to 30.0 : 200.0).

Preparations.—1. *Syrupus amygdalarum* seu emulsivus, almond syrup, a syrup made from sweet almonds, with the addition of bitter almonds and aqua florum aurantii; used as a corrective. 2. *Emulsio amygdalarum composita*, 4 parts amygd. dulc., 6 parts sacch., 1 part magnesia usta.

Poppy oil (*Oleum papaveris*), pressed from poppy seed, has a faint smell, a not unpleasant taste, and resembles the oil just mentioned.

Poppy seed (*Semen papaveris*), of the papaver somniferum, contains 50 per cent poppy oil, 10 per cent albumen; whether also, opium alkaloids, has not yet been ascertained; if so, however, only traces.

Poppy seed, like almonds, can be used for making an emulsio vera, but it has a somewhat disagreeable taste.

Hemp seed (Semen cannabis), from the cannabis sativa, contain hemp seed oil, of which no use is made therapeutically.

Linseed oil (*Oleum lini*), from common flax, linum usitatissimum, is not employed internally. Externally, it is used according to the general indications given for fats (compare page 811 and 814).

Linseed, flax-seed, semen lini, after pressing out the oil, yield the so-called linseed cake or oil-cake (placenta lini) which is much used for poultices. For administration internally (in decoct. 15.0 to 150.0) it may be entirely dispensed with.

The following oils, which are liquid at ordinary temperature, may be employed in a similar manner: nut-oil (oleum nuc. juglandis), rape-seed oil (oleum raparum), cocoanut oil (oleum cocois), which at ordinary temperature is of the consistency of ointment, nutmeg oil (oleum butyrum nucistæ), cacao or chocolate-nut oil (oleum, butyrum cacao), and laurel oil (oleum lauri).

Japanese wax (Cera Japonica) is a vegetable fat of the nature of wax, but its chemical constituents are entirely different (carbono-hydrous). Of similar nature are *paraffine* (obtained by the dry distillation of charcoal and mineral coal) and the fossile paraffine, *ceresine*. These may be employed externally for the same purposes as beeswax.

On account of the large quantity of oil it contains, mention may be here made of

Witch-meal, Semen lycopodii (vegetable brimstone, lycopodium), discharged from the sporules of the club moss, lycopodium clavatum, an extremely fine, light, movable, pale yellow powder, that floats upon water.

The operation of lycopodium taken internally, as far as known, is analogous to that of fat, but its internal use offers no especial advantage. On the other hand it serves as an excellent dusting powder in moist eczema, and is much used as such, and it is a popular remedy in intertrigo of children. Pharmaceutically, it is used as a conspergens for pills.

FATS FROM THE MINERAL KINGDOM.

Vaseline Americanum (saxoleum inspissatum), a fatty substance obtained from the residuum of petroleum, melts at 37°, without taste or smell. It is insoluble in water, partially soluble in alcohol, easily so æther. Mingles with fatty and volatile oils under all circumstances, when fused with them, likewise with glycerine, but separates again upon the addition of water. Muriatic acid and potash lye do not act upon it; nor are the best varieties (the American) changed by the action of nitric acid.

Of late, vaseline has come into use as a very good substitute for fats and glycerine for application upon portions of the skin deprived of the epidermis, in intertrigo, chapped skin, etc., because it causes less irritation and hardly any burning sensation upon the wounded places, and forms a coating over them.

THE CARBO-HYDRATES.

The carbo-hydrates (sugars, starches, gums, and vegetable mucus) are therapeutically of less value than they are for nutritive purposes. The majority of the carbo-hydrates are derived from the vegetable kingdom. They all possess the properties of those various alcohols from which they are derived, and are divided into three groups, according to their composition. Thus we have *grape sugar* ($C_6H_{12}O_6$); *cane sugar* ($C_{12}H_{22}O_{11}$) and *cellulose* ($C_6H_{10}O_5$). Both the latter are easily convertible into the first by fermentation and absorption of water, and consequently should be considered its anhydrates.

VARIETIES OF SUGARS.

Two classes of sugars are distinguished chemically: the first class encomprises those of the formula $C_6H_{12}O_6$, and are grape sugar, fruit sugar, and the so-called lactoses, all of which are separated into alcohol and carbonic acid by fermentation, and furthermore those which are not fermentable, as inosite, sorbine, gum sugar, etc. The second class, of which the formula is $C_{12}H_{22}O_{11}$, is represented principally by cane sugar and sugar of milk, which are primarily inverted, that is, they are converted into members of the first group and then separate into alcohol and carbonic acid.

PHYSIOLOGICAL ACTION.

The physiological influences exercised by the various classes of sugar are almost identical in all regards. Cane sugar and sugar of milk become grape sugar in the intestines, and naturally exert its influence there. The greater part of the sugar in the organism is introduced either as such with food, or as amylaceous substance, which becomes converted into sugar through the action of the saliva and pancreatic juice, while some of the sugar in the organism, such as sugar of milk and inosite, are formed in the tissues.

Disposition in the Body.—A part of the sugar is converted into lactic and butyric acids by the action of the undeveloped intestinal ferments in the stomach and intestines, or perhaps also by formed ferments, such as bacteriæ (Leube). After copious consumption of sugar, the contents of the small intestine show an acid reaction, the upper division containing much lactic acid, and the lower more butyric acid. These acids and the unchanged sugar are rather rapidly taken up by the blood and then are quickly burned into carbonic acid and water. As a consequence, a moderate consumption of sugar is never accompanied by excretion of sugar in the urine, and only the production of carbonic acid

is increased, and thus more carbonic acid is exhaled by the lungs (Gorup-Besanez, Secgen, Pettenkofer, and Voit). It is only when excessive quantities of sugar are consumed, or when pathological conditions prevail (diabetes mellitus and many other diseases), that sugar is found in the urine.

Action.—Sugar provokes its well known sweet taste, which vaeies in intensity according to the kind of sugar tasted. It increases the flow of saliva by reflex action. Prolonged consumption of sugar produces caries of the teeth, especially of those which are denuded of their enamel.

The moderate consumption of sugar provokes no disagreeable disturbances in the organs of digestion; at most it may produce soft stools. When an equable supply of nitrogenized food is maintained, the bodily weight increases.

Large quantities of sugar reduce the appetite and bring about disturbances of digestion, nausea, acid eructations, water-brash, colics, and diarrhœa, all of which are consequences of the excessive formation of lactic and butyric acids.

Exclusive saccharine nutrition produces death in animals, and the symptoms are those of inanition. Stark, who experimented on himself with an exclusive sugar and starch diet, suffered with digestive disturbances, diarrhœa, swelling of the gums, ulceration of the mouth, dermal hemorrhages, emaciation, and it is claimed that he died in consequence of these experiments.

It cannot as yet be positively decided whether the increase of adipose matter which results upon copious consumption of sugar (premising an equivalent introduction of albumen) is brought about by a direct conversion of the carbo-hydrates into fat, or whether this occurs but indirectly through the oxidation of the carbo-hydrates and thus the reduction of the fats and albuminous bodies in the tissues.

THERAPEUTIC APPLICATION.

Sugar enjoys most extensive use as food, and its consideration in this aspect is not requisite, inasmuch as there are no conditions in which it is consumed excessively. Only those states which contra-indicate its use will be mentioned. Catarrhal and especially dyspeptic troubles of the stomach merit first consideration among these, because they incite abnormal fermentation of sugar and increased disturbances of digestion. Diarrhœa and severe diarrhœic

tendencies require as great a limitation of the use of sugar as possible. Marked corpulence is a decided contra-indication to saccharine diet in appreciable quantities, and its exclusion is one of the most important requirements of Harvey's Banting system. Furthermore, in rachitis or osteomalacia it must cede markedly to a preference for nitrogenized matters. The necessity of absolute prohibition of sugar in diabetes mellitus is contested by some observers, but the great majority agree in the importance of as great a limitation as possible, or an absolute prohibition.

The purely medical use of sugar is rather limited. In febrile conditions it is administered as a drink in the form of sweetened water; but aside of the fact that it allays thirst less readily than do acidulated drinks, it must be avoided in diarrhœa and a tendency thereto. Yet it merits consideration because of its nutritive capacity. Large quantities of sugar are especially useful for children, when a light laxitive is required (manna). In poisonings with corrosive substances, especially metals and particularly the salts of copper, and when no more adequate means are at hand, large draughts of sugared water may be given to envelope the toxic matter. Solutions of sugar are often employed in slight acute catarrhs of the respiratory apparatus (laryngeal and bronchial catarrhs) to facilitate extrusion of the secretions. It is extremely doubtful whether they are entitled to credit in this regard. Sugar is most frequently employed as a corrective for drugs which have a disagreeable taste.

It is employed externally as a gentle irritant to atonic ulcers and popularly it is much used in caro luxurians.

Saccharine Remedies.

CANE SUGAR, SACCHARUM ALBUM.

$C_{12}H_{22}O_{11}$ occurs in the juice of nearly all sweet fruits and is particularly abundant in sugar-cane, the sugar-maple, and in many kinds of the beet-root. In the shape of block-sugar it is a colorless aggregation of small crystals, and as rock-candy of large crystals. It is readily soluble in water, but it is taken up slowly and badly by alcohol and does not reduce alkaline cupric solutions.

It is of an intensely sweet taste and is converted into grape sugar in the intestines, and then has all of its physiological and therapeutic tendencies as were detailed in the introductory hereto. Its dose is not fixed; *generally* 15.0 to 30.0 grms, are added to 150 to 200 grm. mixtures, *as a corrective* to taste.

Syrupus simplex seu Saccharis albus, 9 parts of sugar in 5 parts of water.

Syrupus communis is the fluid residue, from cleaning the raffinates.

Sugar of milk, Saccharum lactis ($C_{12}H_{22}O_{11}+H_2O_1$), is found in simple solution only in the milk of mammals, and is probably developed in the mammary glands from the sugar that is introduced as food. It crystallizes in colorless prisms; it is less soluble in water than cane sugar and it reduces alkaline cupric solutions. Its taste is less sweet than that of cane sugar; it is converted into grape sugar in the intestines, and there exercises its characteristic action.

It is entirely superfluous for internal medication. It is claimed that, when used as a purge for infants, it acts better than ordinary sugar, but this is not proven. Its only advantage over cane sugar lies in the fact that it does not absorb atmospheric moisture; therefore, it is preferable to common sugar when used to give body to a powder. Its slight sweetness renders it unavailable as a corrigent for unsavory drugs.

Grape sugar, Glycose ($C_6H_{12}O_6$), though it is the most important sugar, from a phyisological standpoint, is not employed therapeutically.

Maple sugar ($C_6H_{14}O_6$) has been fully discussed.

Honey, mel, the product of the honey-bee, is a mixture of several varieties of sugar (cane, inverted, and especially grape sugar), and contains in addition various constituents of plants, pollen and wax.

Two kinds are distinguished; crude honey (mel crudum), obtained from the comb by pressure, and purified honey (mel depuratum).

Its action is like that of sugar and it may be employed in doses of 50 grms. as a laxative. It is quite frequently used externally; mixed with meal or pure, as a cataplasm for small furuncles; also, especially in connection with sage tea, as a gargle in angina and catarrh of the pharynx, and frequently, especially in connection with borax, painted on aphthæ. The latter application is popular but ineffectual, as it only leads to impurities, which should be specially avoided in aphthæ, and contributes to development of processes of fermentation in the mouth.

Preparations.—1. *Mel rosatum*, rose honey, is made by adding 12 parts of mel depuratum to an infusion of 1 part of roses in 6 parts of water, and evaporating the mixture to the consistency of syrup.

It is only employed externally as a gargle.

2. *Oxymel*, acid honey, consists of 1 part of acidum aceticum dilutum and 40 parts of mel depuratum. An unnecessary preparation, which cannot be used to sweeten medicines.

Licorice-root, radix liquiritiæ (radix glycyrrhizæ) obtained from glycyrrhiza glabra and echinata. The active constituents are grape sugar and a light yellow amorphous glycoside, glycyrrhizin ($C_{24}H_{36}O_9$), which tastes first sweet and then acrid, in addition to asparagine, starch, and organic acids. The physiological action of licorice resembles that of sugar, but is rather more laxative on account of containing glycyrrhizin, which in the pure state acts as a mild laxative when taken in doses of 10 to 15 grms.

The supposed action on the mucous membrane of the mouth and larynx can only be ascribed to the increase of saliva in these parts, as it, like any other kind of sugar, produces a somewhat greater secretion, and the saliva is naturally swallowed with it. The preparation is also of frequent pharmaceutic use as an adhesive ingredient in pills, and as one of the best correctives of many medicines (sal ammoniac, senega, hyoscyamus).

Dosage and Preparations.—1. Radix liquiritiæ glabræ, as such, or in decoction (1 : 150).

2. *Radix liquiritiæ mundata*, given in the same doses.

3. *Succus liquiritiæ crudus*, crude licorice, hard black cylinders. Used alone (1 : 150) or as an addition to many medicines in pills and pastilles.

4. *Succus liquiritiæ depuratus*, purified licorice, is a brown powder used like the foregoing.

5. *Extractum radicis liquiritiæ*, superfluous.

6. *Syrupus liquiritiæ*, obtained by macerating the root, is replaced by sugar and honey. As a corrective (1 : 200) it may be dispensed with.

7. *Elixir succi liquiritiæ* is made by dissolving 1 part each of succus liquiritiæ and ammon. acis. sulfat. in 6 parts of aqua fœnic.

8. *Pasta liquiritiæ* is superfluous.

Carrot root, radix daucii (carrot), from Daucus carota (umbelliferæ), contains very large quantities of cane sugar, mannite, and albuminous substances.

Couch-grass, rhizoma granitis (grass root), from agropyrum repens, granitum, contains 10 per cent of sugar (grape sugar and mannite) extractum granitis, is only used to give consistence to pills.

In addition, the following fruits which contain sugar are occasionally used, but may be dispensed with: *Figs* (cuticæ) and the *arch-bean* (fructus erratonia).

STARCH AND THE AMYLACEOUS SUBSTANCES.

Starch, amylum ($C_6H_{10}O_5$), is found widely extended throughout the vegetable kingdom in grain, legumes, chestnuts, potatoes, most roots and fruit, in the form of characteristically arranged granules in the vegetable cells.

It is insoluble in cold water, alcohol, and ether, and destitute of odor and taste.

In hot water it swells to a pasty mass, which, upon drying, becomes hard and transparent. When heated to 100° starch is converted into dextrine.

It is changed by various ferments (fruit, diastase, fin-saliva, pyralites), fruit, into a somewhat modification (soluble starch), which dissolves in hot and cold water, and then into dextrine, maltose and finally grape sugar.

PHYSIOLOGICAL ACTION.

All kinds of starch, though with different degrees of rapidity, are converted into dextrine and sugar (maltose) by the secretions of the buccal salivary glands. This occurs even when alkaline saliva is neutralized to made acid. The change beginning in the mouth is continued in the stomach, but excess of acid may stop the action temporarily. The gastric juice, on the contrary, without saliva has no such effect, and only assists the digestion of the starch by loosening the connection of the granules. That part of the starch that is not changed in the mouth and stomach is converted into dextrine, maltose, and grape sugar

(musculus) in the small intestine, chiefly by the pancreatic juice. These products are then in part absorbed, in part changed further into lactic and butyric acids. Fresh bile seems to possess no power of converting starch into sugar. The nutritive value of starch and substances containing it is hence the same as that of sugar.

THERAPEUTIC APPLICATION.

The pathological conditions which indicate a diet consisting principally of amylaceous substances, or in which it is used directly as a drug, are about the following: Amylaceous substances form a part of the so called "fever diet." Independently of all theoretical assumptions, it has been empirically agreed, from the time of Hippocrates, to limit nitrogenous food to a minimum in acute fevers, and to give substances containing no nitrogen, especially as amylaceous and saccharine bodies and fats further injure the weakened digestion. Of course this applies especially to febrile conditions of short duration, when the temperature is high, and other symptoms of fever are strongly marked. If the processes which are the basis of the fever are slow, or if symptoms of inanition develop, the so-called "non-stimulating fever diet" no longer suffices, and nitrogenous food must be added.

Secondly, a diet consisting chiefly of the amylacea is suitable in the condition called "Plethora vera," when the patient exhibits no tendency to accumulation of fat, but is still "polychæmic," to use the old clinical expression. Then the quantity of nitrogenous food is diminished, and the diet made to consist chiefly of vegetables and substances containing starch and sugar. This diet also is used empirically with advantage in "acid urinary diathesis," and when there is tendency to arthritis. The amylacea, in suitable forms, also constitute part of the diet in acute inflammatory affections of the mucous membrane of the stomach and intestines.

Certain varieties of starch are often considered of especial benefit in rachitis and scrofulous diseases. It may, however, be regarded as certain that this view is entirely erroneous, and that a diet consisting chiefly of arrow-root does not arrest the processes mentioned.

On the other hand, certain conditions must be considered, which either entirely contra-indicate the amylacea, or greatly restrict their use. These are in fact those that we have already noticed under the head of sugar. First

come chronic catarrhal affections of the stomach, with inclination to acid fermentation; then, a strong tendency to fatty accumulation. Amylaceous diet must further give place to nitrogenous food when the object is to rebuild muscular substance; especially, therefore, after exhausting diseases that have caused much waste of muscular tissue (typhus, suppurations, etc.), and in the period of most rapid growth. According to our own opinion, starch should be entirely avoided in the first year of life. Its use should also be reduced to a minimum in rachitis and scrofulous diseases and in diabetes mellitus.

Starch is used externally in the preparation of enamata that are employed to arrest intestinal discharges and to coat the gut, and it is sprinkled on the skin in intertrigo and eczema; it is also used in starch bandages.

SUBSTANCES CONTAINING STARCH.

Wheat starch, *Amylum tritici*, from Triticum vulgare (Gramineæ).

Potato starch, *Amylum solani*, from Solanum tuberosum, Solaneæ.

Arrow-root, Amylum marantæ, from Maranta arundinacea, Marantaceæ. Arrow-root enjoys a great reputation as food for children. There is no proof whatever that it is any more beneficial than our native varieties of starch; on the contrary, the same contra-indications to its employment prevail which we have mentioned above for the amylaceous substances in general, and which occur especially in children.

If it is given to children, in the absence of any circumstance forbidding its use, it is convenient to stir it into milk or beef-tea, and give a few teaspoonfuls per day. What has just been said of arrow-root is also true of *amylum manihot*, amylum mandiocæ, and other imported varieties of starch. Extended dietetic employment is found for *grana sago*, sago, alone.

Starch gum, *Dextrin* ($C_6H_{10}O_5$), is the product of the action of dilute acids, and the first product of the action of diastose upon starch. In the digestive fluids it is converted, like starch, into grape sugar, but more rapidly than it. Some dextrin must, however, pass into the blood unaltered. According to Ranke and Schiff, the presence of dextrine accelerates the digestion of all kinds of food in the stomach. Dextrin has therefore been tried as a food for children, as in them the saccharifying action of the secretions of the mouth and throat is small, and as dextrine is converted into absorbable sugar much more readily than starch.

Nestle's milk powder, a secret preparation, professedly made of wheat bread and Swiss milk, has its starch already converted into dextrin for the most part. 20 grms. of the powder are ordered to be mixed with 100 grms. of water, and the mixture drunk after heating to 37°C. Nestle's preparation has within the last ten years found extended use as a food for children, and has been recommended by different physicians, Lebert, Kehrer and others. According to our experience it shares the lot of *all the substitutes* for mother's milk, of which others will shortly be mentioned. Some children thrive upon them, others do not. With which

preparation success or failure preponderates, it is difficult to decide, as the statements of individual observers vary greatly.

Jacobi, moreover, quite properly makes the insuperable objection to Nestle's powder that it must be excluded from practice as a secret medicine.

Faust and Schuster's flour for children is more recommendable than the preceding, because its composition is known, at least. It contains 11 per cent of albuminoids, 79 per cent of carbo-hydrates, and 2 per cent of salts.

Liebig's children's food also has part of its starch converted into dextrine, part even changed to sugar. It is prepared as follows: Equal parts (17.5 grms.) of wheat flour and malt ground in a coffee-mill are stirred up with 2.0 grms. of a 14-per-cent solution of carbonate of potassium, 2.0 grms. of water, and 175 grms. of milk. The mixture is heated to 60° to 70° for a long time, in order to convert the wheat starch into sugar by means of the diastose in the malt, and then it is filtered.

Liebig's extract of malt, i.e., barley malt extracted with water, contains 30 per cent of grape sugar, 25 per cent of dextrine, 8 per cent of albuminoids, and 3.5 per cent of ash.

Mere mention may here be made of the many kinds of grain, as well as rice, maize, millet and the legumes, all of which consist chiefly of starch. These are used as food in the most diverse forms (bread, boiled vegetables, beer, etc.), and also employed in more expensive compounds (revalenta arabica, Hoff's preparation).

Vegetable Mucus and Gum.

Vegetable mucus (bassorine) and the various gums ($C_6H_{10}O_5$) are all nearly related vegetable compounds that are always found in nature in combination with potassium, calcium, and magnesium. Vegetable mucus only absorbs water and swells, but the gums are soluble in water. Both, on being heated with nitric acid, are decomposed into mucic, saccharic, acetic, and oxalic acids.

PHYSIOLOGICAL ACTION.

Vegetable mucus and gum dissolve or swell in the digestive fluids. Voit has shown that gum, when dissolved in acid solution of gastric juice, especially in the presence of pepsine, or when dissolved in an alcoholic infusion in the intestines, in the presence of pancreatine, is partly converted into sugar with great rapidity.

He has also proved that vegetable mucus is not changed into sugar, but undergoes acid fermentation, and that both gum and vegetable mucus, together with their products of decomposition, are absorbed. What was formerly doubted, therefore, now seems assured; namely, that both substances possess a definite though very slight nutritive value. Very large quantities cause loss of appetite and a sense of gastric repletion. Their further action is unknown.

THERAPEUTIC APPLICATION.

Mucous substances, especially those prepared in the kitchen (oat-meal gruel, rice-meal gruel), have been for ages a constituent of fever diet in acute febrile affections. According to the preceding statements, we cannot deny them a slight nutritive value; but we have already expressed our opinion, in treating of albuminous food, that the latter can be by no means dispensed with in fevers of long duration and attended by great consumption of tissue.

As direct medicines mucous substances are given in *diarrhœa* of all forms, whether simply catarrhal or attended with ulceration. We cannot determine with certainty that they have the slighest constipating effect. Large doses, undergoing acid fermentation might rather be injurious. We are of the opinion that the benefit in diarrhœa is entirely indirect, as the mucous portion, not usually very cool, renders unnecessary the introduction of water, which would stimulate the peristaltic action by reason of its low temperature.

SUBSTANCES CONTAINING VEGETABLE MUCUS AND GUM.

Salep Root, Tuber Salep.—The tubers of various orchids contain 50 per cent of mucus, 30 per cent of starch, 5 per cent of albuminoids, and 1 per cent of sugar, besides salts.

Salep is given internally according to the above indications. Its importance as a food is entirely subordinate, though it is frequently used as such, especially in the diarrhœas of children.

The form of powder is inconvenient. It is best employed as a decoction in water, milk, or the broth of meat (1 teaspoonful of salep powder to 2 or 3 cups of fluid, 5.0 : 150.0 or 200.0). Mucilago salep, officinal, is used as an addition to mixtures.

Marsh mallow, Radix althææ, from althæa officinalis, malvaceæ, contains nearly equal quantities (30 per cent) of mucus and starch, some asparagin, sugar, fixed oil, and salts, and acts, therefore, like salep root.

1. *Syrupus althææ* is a remedy much employed, especially in popular use, in catarrh of the bronchiæ and larynx, particularly in small children. It has at least the advantage of being harmless.

2. *Species ad gargarisma*, equal parts of fol. althææ, flor. sambuci et malvæ. Used as a gargle.

3. *Species emollientes* is a mixture of equal parts of fol. althææ et malvæ, H. meliloti, flor. chamomillæ, and sem. lini.

Irish moss, Carrageen, a mixture of several marine algæ, contains a very large quantity of mucus, some starch, and traces of iodine and bromine.

Quince seeds, Semen cydoniæ, from cydonia vulgaris, pomaceæ, contain 20 per cent of mucus. Here may also be grouped mallow flowers and

leaves of several species, *flores et folia malvæ*, mullein flowers, flores *verbasci* from *verbascum thapsirfome*, toad-flax, herba Linariæ, from the linaria vulgaris and poppy flowers, flores rhœados from papaver rhoeas.

Gum arabic, *Gummi arabicum* (G. mimosæ), the inspissated juice of several species of acacia (G. mimosæ), dissolves readily in water, and consists chiefly of calcium salts of Arabic acid.

On acidulation with mineral acids and the addition of alcohol, the Arabic acid, also called arabin, $C_{36}H_{60}O_{32}$, may be obtained free from the metal. Gum arabic is very often used externally as an adhesive, and also as a protecting covering in burns and excoriations. It finds frequent pharmaceutic employment in the preparation of emulsions of fat oils, and to hold in suspension substances that are insoluble in water, as sulphaurat. and camphor. It is also used to cover substances that without it would prove local irritants.

Dosage and Preparations.—1. *Gummi arab.*, used internally in powders and solutions (10.0 to 30.0 : 200.0).

2. *Mucilago gummi arabici*, made by dissolving 1 part of gummi arabicum in 2 parts of aqua distillata.

3. *Pulvis gummosus*, 3 parts of gum, 2 parts of pulvis radicis liquiritiæ, and 1 part of sugar.

4. *Pasta gummosa seualthææ*, jujube paste, 200 parts each of gummi arabicum and saccharum, 600 parts of aqua destillata, 150 parts of albumen, and 1 part of ælæosacch. flor. aurantii.

5. *Syrupus gummosus*, 1 part mucilag. gummi to 3 parts of syrupus simplex.

6. *Mixtura gummosa*, 15 parts each of gummi arabicum and saccharum to 170 parts of aqua destillata.

Gum tragacanth, *Gummi tragacantha*, the inspissated juice of several species of astragalus (leguminosæ), a tough, difficultly pulverizable mass of a horny, yellow appearance, is a mixture of mucus and gum, and hence is only partially soluble. Its use is the same as that of gum arabic.

INDEX.

Acetate of morphine, 660
Acetate of potash, 41
Acetate of soda, 42
Acetic acid, 343
Acids, 321
Aconitin, 767
Acorns, 484
Adonis vernalis, 783
Albumen and peptone, 787
Alcohol; spirits of wine, 369
Alcoholic liquors, 384
Alcohols, 362
Alkalies, 13
Alkalies and alkaline earths, 9
Alkaline carbonates, 34
Alkaline earths, 83
Alkaline nitrates, 77
Alkaline phosphates, 50
Alkaline sulphates, 53
Alkaloids, 585
Alkaloids of belladonna, 690
Alkaloids of calabar bean, 710
Alkaloids of cinchona, 590
Alkaloids of hyoscyamus, 690
Alkaloids of jaborandi, 710
Alkaloids of opium, 635
Alkaloids of stramonium, 690
Alkaloids of toadstool, 710
Alkaloid of tobacco, 729
Almond oil, 818
Aloes, 554
Alum, 119
Aluminium, 118
Aluminium and potassium sulphate, 119
Ammonia carbonate, 114
Ammonia compounds, 100
Ammonium carbonicum, 114
Ammoniacum causticum solutum, 106
Ammonium chlorate, 110
Ammonium chloratum, 110
Amyl nitrite, 426
Angelica, 525
Aniline, 451
Anise, 515
Antimony and potassa, tartrate, 249
Antimony—stibium, 249
Apiol, 520
Apomorphine, 681
Apomorphine, 662
Appendix to the alkalies, 83
Appendix to alum, 121
Appendix to copper, 153
Appendix to lead, 136
Appendix to mercury, 223
Appendix to silver, 148
Appendix to sulphur, 307
Appendix to zinc, 160
Appendix to the iodine compounds, 297
Appendix to the alkaline earths, 100
Appendix to the ammonia compounds, 115
Argentum nitricum, 139
Arnica, 525
Aromatic acids, 456
Aromatic anthelmintics, 559
Aromatic compounds, 430
Aromatic cutaneous irritants, 530
Aromatic expectorants, 515
Aromatic nervines, 524
Aromatic oxytoxics, 563
Aromatic plasters and ointments, 528
Aromatics, 517
Arrowroot, 826
Arsenic, 225
Arsenious acid and potassium arsenite, 226
Artemesia, 525

Artemesia, 511
Assafœtida, 526
Atropine and belladonna, 692
Aurantiin, 505
Balsam Peru, 508
Bearberry, 485
Bebeerine, 616
Beer, 388
Beeswax, 818
Benzoic acid, 458
Benzol, 451
Bilberries, 484
Bismuth, 259
Bisulphate of quinine, 615
Bitter almond water, 585
Bitter clover, 574
Bitter almonds, 585
Bitter principles of feeble physiological action, 571
Blisters, 539
Blood, 796
Boric acid, 341
Brandy (distilled liquors), 390
Bromine compounds, 266
Bromine, iodine, chlorine, and their compounds with alkalies, 265
Bromium, 266
Bryonia, 556
Butter, 814
Butternut, 485
Caffein, 617
Calabarin, 720
Calamus, 511
Calcaria chlorata s. hypochlorosa, 300
Calcium and magnesium phosphates, 94
Calcium oxidatum, 85
Calcium oxide and carbonate, 85
Calcium phosphate, 99
Calomel, 214
Campechianum, 485
Camphor, 496
Camphors, 486
Cannabis Indica, 671
Cane sugar, 822
Cantharidal collodion, 542
Cantharides, 539
Capsicum, 515
Carbo-hydrates, 820
Carbon, 307
Carbolic acid, 435
Carbonic acid, 353
Carbonic oxide, 309
Carbonate of lithium, 40
Carbonicum oxidatum, 309
Cardui benedictus, 576
Cardol, 543
Carrageen, 828
Carraway, 511
Carrot, 824
Cascarilla, 513
Castor oil, 556
Castoreum, 528
Catechu, 485
Cathartic aromatics, 543
Caustic alkalies, 32
Caustic ammonia, 106
Caustic potash, 32
Caustic soda, 32
Cetaceum, 818
Chamomile, 520
Cherry laurel, 585
Cherry laurel water, 585
Cherry water, 585
Chinchonidin, 591
Chinchonine, 591
Chinese tea, 629
Chinioideum, 615
Chinovin, 591
Chloral hydrate, 414
Chlorate of potash, 74
Chlorine, chlorinated water, 298
Chlorine compounds of the Alkalies, 58
Chloride of sodium, 58
Chloride of zinc, 159
Chloroform, 394
Chocolate, 630
Chonchinine, 615
Chromic acid anhydride, 340
Chrysarobin, 453
Chrysophanic acid, 453
Cinchona, 523
Cinchonia, 615
Cina, 559
Cinnamon, 512
Citrate of iron and quinine, 615
Citric acid, 347
Citron oil, 505
Clover, 507
Cloves, 513
Coca, 635
Cocaine, 630
Cocoa, 630
Cod-liver oil, 814
Codeine, 661
Coffee, 624

Coffee, Tea, Guarana, Cocoa, and Coca, 616
Colchicine, 689
Colocynth, 555
Columbo, 577
Compound ipecac powder, 669
Condensed milk, 798
Condurango, 577
Conium, 746
Copaiba, 518
Copper, 149
Corrosive sublimate, 209
Coto bark, 678
Couch-grass, 824
Cowslips, 521
Creasotum, 454
Croton oil, 556
Cubebs, 518
Cuprum sulphuricum purum, 125
Curare, 739
Curled mint, 571
Cyanogen compounds, 578
Dammara, 529
Dextrin, 826
Dichonquinine, 591
Dicinchonin, 591
Digitalis purpurea, 771
Diuretic and diaphoretic aromatics, 517
Eggs, 795
Elaterium, 556
Elemi, 529
Emetine, 684
Ergot, 563
Ether, 410
Eucalyptol, 506
Eucalyptus, 506
Extract of opium, 669
Farfara, 577
Fats, 807
Fennel seed, 516
Flavoring agents, 504
Formic acid, 343
Fruits, 348
Galbanum, 529
Galeopsidis, 577
Gallic acid, 476
Garden thyme, 511
Garlic, 539
Gelsemium sempervirens, 675
General considerations, 363
Gentian root, 574
Ginger, 512
Glutinous substances, 801
Glycerine, 803
Glycerine and fats, 803
Glycosides with strong physiological action, 769
Grape sugar, 823
Green hellebore, 783
Guaiac, 523
Guanidin, 116
Guarana, 629
Gum arabic, 829
Hæmostatic iron compounds, 184
Hemp oil, 819
Herba centaurii, 575
Honey, 823
Hydrochloric acid, 336
Hydrocyanic acid, 579
Hydrofluoric acid, 341
Hydrogen, 309
Hydrogen peroxide, 309
Hydrogenium peroxidatum, 309
Hydrogenium sulphuratum, 301
Hydrargyrum bichloratum corrosivum, 209
Hydrargyrum chloratum mite, 214
Hydrargyrum depuratum, 222
Hyoscyamine, 708
Iceland moss, 576
Inorganic and the organic (fatty) acids, 321
Iodine, 278
Iodine compounds, 278
Iodum, 278
Ipecac, 686
Iron, 161
Iron combinations and mixtures with other metals, 187
Iron compounds, 184
Iron compounds as antidotes, 187
Iron tinctures, 183
Jalap, 553
Juniper, 519
Kali hydricum seu causticum, 32
Kalium aceticum, 41
Kalium bromatum, 267
Kalium chloratum, 74
Kalium chloricum, 74
Kalium iodatum, 284
Kalium nitricum, 79
Kalium sulphuratum, 305
Kalium tartaricum et bitartaricum, 42
Kamala, 562
Kinic acid, 591
Kino, 485

Kinotannic acid, 591
Kosso, 562
Kresotinic acid, 476
Kumys, 392
Lactic acid, 349
Lactucarium, 674
Laudanum, 669
Lard, 814
Lead acetate, 132
Lead and its compounds, 121
Lead carbonate, 135
Lemon oil, 505
Licorice, 823
Lime chloride, 300
Lime flowers, 521
Lime phosphate, 99
Linseed oil, 819
Liquor natrii hydrici seu caustici, 32
Lithium carbonicum, 40
Lithium compounds, 31
Lobelia, 738
Lupulin, 674
Lycopodium, 819
Mace, 513
Magnesia carbonate, 92
Magnesia oxide, 91
Magnesia sulphide, 93
Magnesium carbonicum, 92
Magnesium oxidatum, 91
Magnesium sulphuricum, 93
Malic acid, 346
Manganese, 189
Manna, 559
Maple sugar, 823
Marsh mallow, 828
Mastich, 529
Matico, 518
Meat, 793
Melissa leaves, 521
Mercury, 191
Metalloids, arsenic, phosphorus, antimony, bismuth and nitrogen, 224
Metals, 116
Mezereum, 542
Milk, 796
Millefolia, 575
Mineral acids, 333
Morphine, 636
Moschus, 527
Muriate of morphine, 660
Muriate of quinine, 615
Muscarine, 725
Musk, 527
Mustard seed, 536
Myrrh, 517
Myrtle bilberries, 484
Narceine, 661
Narcotine, 660
Natrium aceticum, 42
Natrium bromatum, 276
Natrium carbonicum et bi-carbonicum, 39
Natrium chloratum, 58
Natrium iodatum, 297
Natrium nitricum, 77
Natrium phosphoricum, 52
Natrium sulphuricum, 53
Natro-kalium tartaricum, 42
Nicotine, 729
Nitrate of silver, 139
Nitric acid, 335
Nitro-benzol, 452
Nitrogen, 261
Nitrogen oxide, 261
Nitrogen suboxide, 262
Nitrogenium oxidatum, 261
Nitrogenium suboxidatum, 262
Nutgalls, 484
Nutmeg, 513
Nux vomica, 747
Oak bark, 484
Oil of bergamot, 505
Oil of cade, 456
Oil of lavender, 506
Oil of orange flowers, 505
Oil of orange peel, 505
Oil of rosemary, 506
Oil of roses, 505
Oil of turpentine, 488
Olive oil, 818
Oleum ricini, 556
Oleum tiglii, 556
Opium, 662
Organic (fatty) acids, 342
Oxalic acid, 351
Ox bile, 577
Oxide, calcium, 85
Oxide, carbonate, and vegetable acid compounds of magnesium, 90
Oxide of lead, 136
Oxide of zinc, 156
Oxygen, 310
Pancreatine, 801
Pansy, 520
Paraguay tea, 629
Parasiticides, 508

Paregoric, 669
Parsley, 520
Pepper, 514
Peppermint, 511
Pepsine, 800
Permanganate of potash, 180
Phlorrhizin, 577
Phosphate of soda, 52
Phosphate of lime and magnesia, 94
Phosphoric acid, 336
Phosphorus, 240
Physostigmine, 712
Picric acid, 452
Picrotoxin, 786
Pilocarpine, 720
Pimpinella, 517
Pine resin, 528
Piper album, 514
Piper nigrum, 514
Piperine, 616
Plants containing tannic acid, 484
Plumbum aceticum, 132
Plumbum carbonicum, 135
Plumbum hydrico-aceticum solutum, 134
Plumbum oxidatum, 136
Polygala amara, 577
Pomegranate, 561
Poppy oil, 819
Potash chlorate, 74
Potassium bromide, 267
Potassium chlorate, 74
Potassium chloride, 74
Potassium compounds, 21
Potassium hypermanganicum, 180
Potassium iodide, 284
Potash nitrate, 79
Potassium sulphate, 305
Propylamine, 115
Proteine matters, 787
Punica granatum, 561
Pure iron compounds, 180
Pyrethri Germanici, 511
Pyrogallic acid, 452
Quassia, 575
Quebracho, 679
Quinine, 590
Radix iridis, 506
Resin of ammoniac, 517
Resina benzoes, 505
Rhatany, 485
Rheum, 551
Rhoeadine, 662
Rhubarb, 551
Roman chamomile, 521
Rue, 570
Ruta, 570
Sabina, 569
Sabine, 569
Saffron, 514
Salep, 828
Salicin, 475
Salicyl cotton, 475
Salicyl water, 475
Salicylic acid, 463
Salts of the alkalies with the fatty acids, 81
Salts of the alkalies with the vegetable acids, 41
Salvia, 485
Sambucus, 521
Santonine, 559
Saponine, 783
Saponis, 81
Sarsparilla root, 521
Sassafras, 523
Scammony, 554
Secale cornutum, 563
Senega, 783
Senna, 550
Silver, 137
Simaruba, 577
Soda carbonate and bicarbonate, 39
Sodium benzoate, 460
Sodium bromide, 276
Sodium chloride, 58
Sodium compounds, 18
Sodium iodide, 297
Soda nitrate, 77
Sodium salicylate, 469
Sodium santonate, 561
Solanine, 787
Solution chloride of antimony, 259
Sparteine, 746
Spices, 509
Squills, 782
Stramonium, 709
Staphisagria, 767
Starch, 824
Stibium chloratum solutum, 259
Stibium-kalium tartaricum, 249
Stibium sulphuratum aurantiacum, 258
Strychnine, 747
Styrax balsam, 509
Succinic acid, 352
Sugar, 820

Sugar of milk, 823
Sulphate of cinchonia, 615
Sulphate of copper, 152
Sulphate morphine, 660
Sulphate of quinine, 614
Sulphate of soda, 53
Sulphate of zinc, 158
Sulphur, 305
Sulphur and its compounds, 301
Sulphuretted hydrogen, 301
Sulphuric acid, 333
Sulphurous acid, 341
Tallow, 814
Tamarind, 559
Tanacetum, 561
Tannate of quinine, 615
Tannic acid, 477
Tansey, 561
Tar, 455
Taraxicum, 576
Tartaric acid, 347
Tartrate of potash and soda, 42
Tartrate soda and potash, 42
Taxus, 570
Terpenes, 486
Tetanic alkaloids of ignatius, 747
Tetanic alkaloids of opium, 747
Tetanic alkaloids of strychnos, 747
Thebaïne, 662
Theobromine, 629
Thuja, 570
Thymol, 453
Tincture cinchona, 616
Tincture opium, 669
Tobacco, 734
Tolu balsam, 509
Tormentilla, 485
Tragacanth, 829
Trimethylamine, 115
Unguentum hydragyri cinereum, 219
Valerian, 524
Valerianate of quinine, 615
Valerianic acid, 346
Vanilla, 513
Vaseline, 819
Vegetable mucus and gum, 827
Veratrine, 758
Virginia snake root, 525
Volatile etherial oils, 486
Wild thyme, 511
Wine, 384
Wine of cinchona, 616
Wood infusions, 521
Wood tea, 524
Wood vinegar, 456
Wormwood, 525
Whey, 798
White glue, 803
Yellow sulphide of antimony, 258
Zinc, 154
Zincum chloratum, 159
Zincum oxidatum, 156
Zincum sulphuricum, 158

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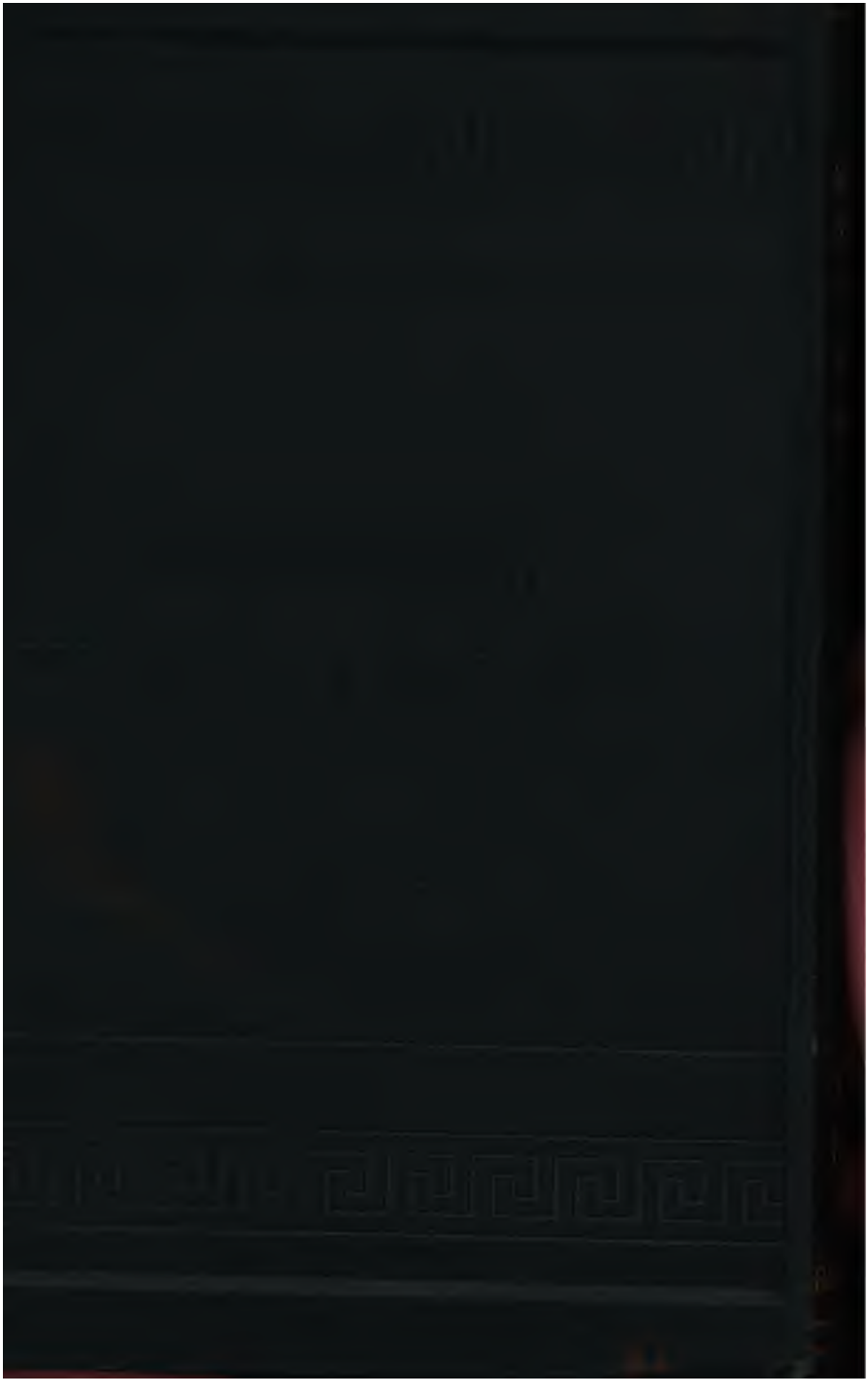
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